OUTCOME OF GLAUCOMA SURGERY IN PATIENTS ON PROSTAGLANDIN ANALOGUES

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CERTIFICATE

This is to certify that this dissertation entitled "**Outcome of glaucoma surgery in patients on prostaglandin analogues**" submitted to the Tamil Nadu Dr MGR Medical University, is a bonafide work done by **Dr Aswin P.R, M.B.B.S**, under our guidance and supervision in the Glaucoma department of Aravind Eye Hospital and Post-Graduate Institute of Ophthalmology, Madurai during his residency programme from May 2016 – June 2017.

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DECLARATION

I, **Dr. Aswin. P.R** solemnly declare the dissertation titled **"Outcome of glaucoma surgery in patients on prostaglandin analogues"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other university board either in India or abroad. This dissertation is submitted to the **Tamil Nadu Dr. M. G. R. Medical University**, Chennai in partial fulfilment of the rules and regulation for the award of **M. S. Ophthalmology (BRANCH III)** to be held in May 2018.

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CONTENTS

PART – I

INTRODUCTION

Glaucoma is the second leading cause of irreversible blindness worldwide with an estimated 60.5 million affected by the disease in 2010 and 12 million people estimated to be blind due to it.(1) India is home to 12 million with Glaucoma and 1.5 million blind due to it as per the major prevalence studies in India in the recent past.(2–7)

Glaucoma by definition is “a group of disorders of multifactorial aetiology united by a clinically characteristic optic neuropathy with potentially progressive clinically visible changes at the optic nerve head, comprising focal or generalized thinning of the neuroretinal rim with excavation and enlargement of the optic cup, representing neurodegeneration of retinal ganglion cell axons and deformation of the lamina cribrosa, with corresponding diffuse and localized nerve fibre bundle pattern visual field loss..”(8) When the treatment is considered, IOP reduction is the only current evidence-based treatment strategy in all types of glaucoma and reduction in IOP is proven to reduce the progression of the disease (9–14).

According to the AAO practice guidelines, the treatment goals in glaucoma include achieving a stable optic nerve or retinal nerve fibre layer status, controlled IOP and stable visual fields while maintaining quality of life.(15) Most clinicians begin treatment with medical therapy

before considering laser or surgical therapy. This have been attributed to multiple clinical trials on medical therapy first showing comparable results to primary incisional surgery.(16,17) Ocular hypotensive therapy, due to the possibility of producing systemic side effects, other therapeutic options are currently preferred, with prostaglandin analogues being one of the most widely used (18) However, though multiple studies have shown the negative effects of long-term topical therapy on the ocular surface which affects the outcomes of subsequent filtration surgery, there is no conclusive evidence on whether prostaglandin analogues cause increased failure rates compared to other drugs. (19–23) It was to address these lacunae in medical literature the following study was conducted.

THEORY

FUNCTIONAL ANATOMY

The ciliary body, the trabecular meshwork and the uveoscleral pathway are the main structures involved in aqueous humour physiology.

The ciliary body is triangular in cross-section with its apex directed posteriorly towards the ora serrata and the base giving rise to the iris. Thus it bridges the anterior and posterior segments. The 2 principal functions of the ciliary body are: 1. Aqueous humor formation and 2. Accommodation.

It is attached at its base to the scleral spur. It is 6-7 mm wide and has 2 parts: 1. Pars plana (extends posteriorly from ora serrata to the cilary processes) and 2. Pars plicata (richly vascularised anterior part) consisting of radial folds called cilary processes which are the sites of aqueous humor formation. The ciliary processes have 2 layers of epithelium: inner non-pigmented layer and outer pigmented layer which lie with its apical surfaces apposed to each other by a complex system of junctions and cellular interdigitations.(24,25) The blood aqueous barrier is maintained by the presence of tight junctions (zonulae occludentes) along the lateral intercellular spaces. The non-pigmented epithelium has multiple basal infoldings, large nuclei, mitochondria, extensive

endoplasmic reticulum and Golgi complexes as they play a crucial role in aqueous production.

The role of ciliary body in accommodation is brought about by the ciliary muscle which consists of 3 layers of fibres which function as a unit: 1. The outer longitudinal fibres, 2. the middle radial fibres and 3. The innermost circular fibres. The ciliary body is supplied by both sympathetic, parasympathetic and sensory nervous systems. The sympathetic fibres originate from the superior cervical ganglion and carotid plexus while the parasympathetic fibres come from the Edinger-Westphal nucleus and pterygopalatine ganglion. The sensory fibres which arise from the trigeminal ganglion come via the ophthalmic nerve.(26)

The trabecular meshwork has been described as a circular sponge work of tissue that is triangular in cross-section, lined by trabeculocytes and forms the major part of the conventional outflow system. It can be divided into 3 components: 1. Uveal, 2. Corneoscleral, and 3. Juxtacanalicular meshwork. (27)

The uveal meshwork extends from the iris root and ciliary body to the peripheral cornea and forms the lateral border of the anterior chamber. It is composed of cord-like trabeculae with irregular apertures measuring between 25 to 75μm.

The corneoscleral meshwork extends from the scleral spur to the anterior wall of the scleral sulcus forming the major part of the trabecular meshwork. It consists of a series of thin, flat, perforated connective tissue sheets arranged in a laminar pattern which become progressively smaller nearing the Schlemm's canal.

The juxtacanalicular meshwork forms the outermost part and is composed of a layer of connective tissue line on either side by endothelium. The outer endothelial lining forms the inner wall of the Schlemm's canal. This region contributes to maximum of the outflow resistance not only due its narrowness and tortuosity but also the resistance offered by extracellular proteoglycans and glycoproteins. (28)

Schlemm's canal is a circular tube lined by endothelial cells and surrounded by connective tissue. From the Schlemm's canal arise around 20-30 collector channels which drain into the deep and midscleral venous plexus.

Physiology of Aqueous Humour Production and Outflow

The aqueous humor provides a clear medium between the cornea and the lens, provides nutrition and removes metabolic wastes to both these structures. It also plays a role in neurotransmitter transport, homeostasis, drug transport and inflammatory reactions. The inflow and

outflow of aqueous humor regulates the intraocular pressure. The rate of inflow is approximately 2.4±0.6µL/min in the adult eye.(13)The aqueous humour is produced by the non-pigmented epithelium of the ciliary body by 3 important processes– Ultrafiltration, Active transport and Diffusion.

The process by which fluid and its solutes cross a semipermeable membrane under a pressure gradient is called ultrafiltration. Diffusion is movement of the substance across a membrane along its concentration gradient. The pressure gradient here is between the capillary pressure and the interstitial fluid pressure (IOP) which promotes fluid movement. Diffusion and ultrafiltration are responsible for the accumulation of plasma ultrafitrate in the stroma, behind tight junctions of the non-pigmented epithelium, from which the posterior chamber aqueous humor is derived

The high concentration of colloids in the tissue space of the ciliary process however retards fluid movement from the stroma into the posterior chamber. Ultrafilration and diffusion thus can move fluid out of the capillaries into the stroma but by itself is not enough to produce the entire amount of fluid in the posterior chamber due to the resistance provided by the large colloidal oncotic pressure differential. Thus ultrafiltration moves fluid out of the cells into the stroma but requires an active metabolic process to bring it to the posterior chamber. (29)

The active transport is an energy-dependent process that selectively moves a substance against its electrochemical gradient across a cell membrane which occurs in the non-pigmented part of the ciliary epithelium and accounts for approximately 80% to 90% of the aqueous produced in the posterior chamber. (30,31) The selective trans-cellular transport of anions, cations and other molecules across a concentration gradient in the blood aqueous barrier by the non-pigmented ciliary epithelium creates the sufficient osmotic forces to attract water thus forming the aqueous humor. This is mediated by protein transporters distributed in the cell membrane and the energy required for the transport is generated by hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP), which is activated by Na+ and K+ mediated by Na+-K+-ATPase, an enzyme located in both the non-pigmented and pigmented ciliary epithelia

The outflow of aqueous from the eye occurs through 2 pathways. The conventional pathway consisting of the trabecular meshwok, passing through the Schlemm’s canal and reaching the aqueous and episcleral veins via the collector channels. The non-conventional route is formed by the uveoscleral pathway where the aqueous enters the connective tissue between the muscle bundles, passes through the suprachoroidal space and exits through the sclera.

The balance between the production and drainage of aqueous humor is what maintains the intraocular pressure. Elevation of IOP usually occurs due to the disrupted aqueous outflow through the convention pathway and this is a major risk factor for glaucoma.(13)

Intraocular pressure

Intraocular pressure which was earlier considered the aetiology behind glaucoma is now being recognised as the only modifiable risk factor and is by far not the only risk factor.(15)It is regulated by the aqueous outflow system which has been explained in the previous section. Defects in this system can arise from chronic oxidative stress and/or from gene mutations. (32–34)The resultant increase in IOP is believed to cause mechanical deformation of the cribriform plates of the lamina cribrosa which in turn compress the optic nerve bundle causing glaucomatous changes in the optic nerve.(35)The trabecular meshwork has been demonstrated to show cytoskeletal changes, altered cellularity and changes in the extracellular matrix by multiple investigators. (36–40)It has been proven that IOP plays an important role in the neuropathy in POAG and reduction in the IOP reduces the risk of visual field progression in open-angle glaucoma.(12,14,16,17,41–44)A significant positive correlation has also been observed between the duration and

level of IOP and retinal ganglion cell loss with up to 50% loss seen during the initial 2-3 months of IOP elevation.(45–49)

However, the relationship between elevated IOP and glaucomatous optic neuropathy is highly variable. (9–11,50) Studies have shown only up to 10% of patients with elevated IOP show signs of visual field loss and instances where up to 61% of patients with low IOP (<21 mmHg) show glaucomatous disc and vision field changes.(51,52). Thus IOP though playing a key role in the pathogenesis of glaucoma cannot be considered as the sole etiology as it was previously considered but rather an important causative dose related risk factor.

Pathology of glaucoma

Glaucoma is currently considered more as an optic nerve disorder in which the intraocular pressure is only one of the many risk factors. All glaucomatous optic atrophy has been described in textbooks to have the following features in common: 1. progressive death of retinal ganglion cells, 2. characteristic excavation of the optic nerve head or cupping and 3.corresponding, functionally apparent, sequential, visual field deterioration in characteristic patterns. The pathophysiology of glaucoma, though not understood fully, is related to retinal ganglion cell death which is related to the intraocular pressure. The death of RGCs has been shown in animal eyes and patients with glaucoma as taking place in 2 phases: in

the first phase by apoptosis which is followed by a second phase neuronal loss due to the toxic effect of the degenerating axons in addition to continued exposure to elevated IOP. According to various theories, factors like elevated IOP and vascular dysregulation, contribute primarily in the form of obstruction to axoplasmic flow, altered laminar glial and connective tissue and microcirculatory changes at the laminar level during the initial stages. The glutamate or glycine released from the injured neurons and oxidative damage caused by nitric oxide and other reactive oxygen species causes further damage. This is followed by deformation and backward bending of the lamina cribrosa along with astrocyte and microglial activation at the ONH which results in the pathognomonic excavation and enlargement of the optic cup where there is death of the axons associated with loss of ganglion cells, with focal or generalized thinning and undermining of the neuroretinal rim.

The excavation of the optic nerve head or cupping seen in glaucoma has been described as due to 1.loss of neural rim axons, 2. elongation, stretching and collapse of the laminar beams and posterior bowing and 3. outward, centrifugal rotation of the laminar insertion into the scleral insertion zone.(53,54) these structural changes to the neurons produce corresponding functional changes like field defects.

Classification of glaucoma

Glaucoma can be classified into various types based on the presentation (Open angle / Closed angle), facility of aqueous outflow (pupillary block / without pupillary block) and presence / absence of other factors contributing to progressive vision and visual field loss (Primary / Secondary). Accurate treatment guides the treatment of glaucoma.

I. Angle closure glaucoma

A. Primary angle closure disease

1. Natural history

   i. Primary angle closure suspect

   ii. Primary angle closure

   iii. Primary angle closure glaucoma

2. Anterior segment mechanism of closure

   i. Iris-pupil obstruction eg. Pupillary block

   ii. Ciliary body anomalies eg. Plateau iris syndrome

   iii. Lens-pupil block eg. phacomorphic block

B. Secondary angle closures

1. Anterior pulling mechanisms

   i. Neovascular glaucoma

   ii. Iridocorneal endothelial syndrome

iii. Posterior polymorphous dystrophy

iv. Aniridia

v. Penetrating keratoplasty

vi. Epithelial downgrowth

vii. Fibrous ingrowth

viii. Flat anterior chamber

2. Posterior pushing mechanisms

i. Ciliary block glaucoma

ii. Cysts of the iris and ciliary body

iii. Intraocular tumours

iv. Nanophthalmos

v. Suprachoroidal haemorrhage

vi. Intravitreal air injection

vii. Ciliochoroidal effusions

viii. Scleral buckling procedure

ix. Retrolental fibroplasia

II. Open-angle glaucoma

A. Primary open-angle glaucoma

1. IOP higher than normal range

2. IOP within normal range (Normal-tension glaucoma)

B. Secondary open-angle glaucoma

1. Pigmentary glaucoma
2. Pseudoexfoliation glaucoma
3. Steriod induced glaucoma
4. Lens-induced glaucoma
    i. Phacolytic
    ii. Lens-particle glaucoma
    iii. Phacoanaphylaxis
5. Glaucoma after cataract surgery
    i. α-chymotrypsin glaucoma
    ii. Glaucoma with viscoelastics
    iii. Pigment dispersion and intraocular lens induced
    iv. UGH syndrome
    v. Glaucoma post Nd-YAG laser posterior capsulotomy
    vi. Glaucoma with vitreous in anterior chamber
6. Glaucoma after trauma
    i. Chemical burns
    ii. Electric shock
    iii. Radiation
    iv. Penetrating injury
    v. Contusion injury

7. Glaucoma associated with intraocular haemorrhage
    i. Ghost cell glaucoma
    ii. Haemolytic glaucoma
    iii. Haemosiderosis
8. Glaucoma associated with Retinal detachment
9. Glaucoma after vitrectomy
    i. Intraocular gas
    ii. Intraocular silicone oil
10. Glaucoma with uveitis
    i. Fuchs heterochromic iridocyclitis
    ii. Glaucomatocyclitic crisis
    iii. Trabeculitis
    iv. Herpes simplex
    v. Herpes zoster

Primary Open Angle Glaucoma

Primary open angle glaucoma is a chronic progressive optic neuropathy with characteristic pattern of optic nerve damage and corresponding visual field loss which develops in the presence of open anterior chamber angles. It manifests by cupping and atrophy of the optic disc in the absence of other obvious causative ocular or systemic conditions known to cause glaucomatous disease. Elevated IOP is an

important risk factor for POAG along with other risk factors such as lower ocular perfusion pressure, race, low central corneal thickness, advanced age and positive family history.

The major theories for optic disc damage in POAG are –

1. Onset of vascular dysfunction causing ischemia to the optic nerve
2. Mechanical dysfunction via compression of the axons within lamina cribrosa

The cause of raised IOP in POAG is due to the resistance to aqueous outflow –suggested by multiple theories like

1. Trabecular meshwork by accumulated material.
2. Loss of trabecular endothelial cells.
3. Reduction in pore density and size in the inner wall of endothelium of Schlemm's canal.
4. Loss of giant vacuoles in the inner wall endothelium of the Schlemm's canal.
5. Loss of normal phagocytic activity.
6. Disturbance of neurologic feedback mechanism.

Pseudoexfoliation glaucoma

Pseudoexfoliation syndrome is characterised by slit-lamp visualization of white powdery fibrillar material (PXF material) in the anterior segment of the eye. Mutations in the LOXLl, seem to be present in nearly all cases of exfoliation syndrome and exfoliation glaucoma. Histologically, this material has been found in and on the lens epithelium and capsule, pupillary margin, ciliary epithelium, iris pigment epithelium, iris stroma, iris blood vessels, and subconjunctival tissue.

The chamber angle is often characterized by a trabecular meshwork that is heavily pigmented with brown pigment, usually in a variegated fashion along with an inferior pigmented deposition, scalloped in nature, present anterior to the Schwalbe line called the Sampaolesi line.

The mechanism by which pseudoexfoliation causes glaucoma is congestion of the trabecular meshwork by the fibrillar material causing Open angle glaucoma and the zonular laxity causing angle closure glaucoma. The mean IOP is also higher in affected PXF glaucoma individuals compared with primary open angle glaucoma patients with IOPs that also fluctuate more widely. Those individuals who have glaucoma at the time of diagnosis often not only have higher pressures, but also have more severe optic nerve damage compared to POAG.

Management of Glaucoma

The visual impairment caused by Glaucoma is irreversible and the loss of peripheral vision, depth perception and contrast sensitivity has a major effect on an individual's life. The treatment goals, according to AAO practice guidelines, include achieving a stable optic nerve or retinal nerve fibre layer status, controlled IOP and stable visual fields while maintaining quality of life. (15) The only way currently available and proven to slow or stop progressive glaucomatous damage is reducing the intraocular pressure below the level at which further damage to the optic nerve does not take place. Achieving this "target-pressure" is dependent on the patient - based on initial IOP, severity of damage, age, compliance and reasonable expectations. This needs to be continually reassessed and reset based on the clinical course.

The currently available modalities in attaining this target-IOP include medical therapy, laser trabeculoplasty, surgical options and cyclodestructive procedures. While multiple large-scale randomised studies have shown local treatment – either medical or surgical – lowers the intraocular pressure and prevents further visual field loss to a statistically significant extent in POAG, and OHT, the available evidence does not suggest which modality to be used as the first choice or when

should a patient who has been medically treated undergo surgery. (17,42,44)

Most clinicians begin with medical therapy, then go on to laser surgery, and finally perform incisional surgery if the IOP is not adequately controlled. This stepwise process reflects the safety and efficacy of the treatments for the individual patient.

Conversely several clinical trials have studied using laser first or incisional surgery first and have obtained comparable results to primary medical therapy. (16,17,55)

Medical therapy – Antiglaucoma agents

The mainstay of treatment of over a century, owing to its safety, reliability and simplicity, majority of patients respond well to topical Antiglaucoma agents. More over being relatively cheaper and without the obvious risks associated with surgery, most patients prefer medical management initially. The Collaborative Normal tension Glaucoma Study (CNTGS) and the Early Manifest Glaucoma Trial both showed that reducing intraocular pressure had a positive effect by reducing the risk of visual field progression in open angle glaucoma. The Collaborative Glaucoma Initial Therapy Trial at the end of 5 years showed no difference in the progression of visual field loss with medical or surgical

management. Though the quality of life was equal in both groups, the local side-effects were more among the medically treated while the incidence of cataract and reduced visual acuity more following surgery. (12,14)

As explained in-detail in subsequent sections, due to the inflammatory reaction induced by long term topical therapy, medically treated eyes may not have as good a success rate following filtering surgery when compared to eyes treated with primary surgery.(21,22,56) Other problems associated with topical medical management were the possible local and systemic side-effects. Lastly there is the issue of compliance which is extremely important especially in a chronic disease condition like glaucoma.

Topical Antiglaucoma agents can be divided into 5 classes

1. **Adrenergic receptor antagonists**
    - Timolol, Betaxolol, Levobunolol, Carteolol, Metoprolol
2. **Adrenergic agonistis**
    - Non Selective – Epinephrine, Dipivefrine
3. **Cholinergic agents**
    - Direct acting – Pilocarpine
    - Indirect acting – Echothiophate iodide, Demecurium bromide, Physostigmine, Neostigmine

4. **Prostaglandin analogues**
    - Latanorpost, Bimatoprost, Travoprost, Unoprostone, Tafluprost
5. **Carbonic anhydrase inhibitors**
    - Dorzolamide, Brinzolamide

Cholinergic agents

The first Antiglaucoma medication to be introduced was the calabar bean which turned out to be the original source for Physostigmine, a potent miotic. The IOP lowering effects and ability to break angle closure attacks were not appreciated till later in 1876 when it was reported by Laqueur and Weber independently. Weber was also the reason behind Pilocarpine, the second miotic, which still holds a place as an adjunctive therapy even a century since its introduction.

Mechanism of action

- Open angle glaucoma - acts on the muscarinic receptors in the smooth muscles and causes contraction of the ciliary muscle which produces traction on the scleral spur and displaces it posteriorly. This in turn causes further traction on the trabecular meshwork resulting in separation of the trabecular sheets and prevents the Schlemms canal from collapsing. Thus increasing aqueous outflow in open angle glaucoma.

- Angle closure glaucoma – Pilocarpine causes pupillary constriction by stimulating the muscarinic receptors on the iris sphincter. This pulls the iris root away from the angle and improves outflow in angle closure.

Uses

- Angle Closure glaucoma – to treat acute angle closure attack and facilitate laser iridotomy
- Peripheral iridotomy - to achieve miosis prior to laser iridotomy
- Plateau iris – to prevent synechial angle closure.

Side-effects

- Functional - Brow ache, Induced myopia, Punctal stenosis, Miosis leading to diminished vision and constricted fields
- Anatomical - Conjunctival congestion, Cataract, Rhegmatogenous Retinal detachment, Increased blood aqueous barrier permeability

Contraindications

- Active anterior uveitis
- Rubeosis iridis
- Extensive angle closure with very less conventional outflow– Pilocarpine can paradoxically elevate IOP by reducing the uveoscleral outflow

- High myopia
- History of retinal detachment
- Peripheral retinal degeneration

Adrenergic agonists

Epinephrine was introduced in 1901 when Jean Darrier first discovered its IOP lowering property and first described its role as an adjunct along with Pilocarpine as an Antiglaucoma medication.

The non-selective adrenergic agonists like Epinephrine and Dipevefrin act by reducing the aqueous production as well as by increasing both the conventional and uveo-scleral outflow. Although effective the non-selective adrenergic agonists have been largely replaced by selective alpha receptor agonists like Brimonidine, Apraclonidine and Clonidine.

Mechanism of action

- Reduces aqueous production
- Reduces episcleral venous pressure (Clonidine)
- Increased outflow facility
- Increased uveoscleral outflow (Brimonidine)
- Neuroprotection (Brimonidine)

Uses - Long term management of Open angle glaucoma and ocular hypertension

Side-effects

- Allergic conjunctivitis (Brimonidine)
- Dry mouth
- Somnolence

Contraindications – children and infants – Can cause CNS depression with risk of bradycardia, hypotension, seizures and apnoea.(67-68)

Carbonic anhydrase inhibitor

Acetazolamide first appeared in early 1950s and by 1954 its potent IOP lowering effect was known. However it had a number of unpleasant side effects and the topical formulation had little to no effect on IOP. The search for topical carbonic anhydrase inhibitors was nearly abandoned till Dorzolamide was marketed in 1995 by Merck Research Laboratories as a potent and safe Antiglaucoma agent. The second topical CAI was named Brinzolamide and marketed by Alcon Laboratories after FDA approval.

Mechanism of action – lower intraocular pressure by decreasing aqueous production by inhibiting carbonic anhydrase II isoenzyme in the ciliary epithelium

Indications – mainly as second line and adjunctive therapy due to thrice daily dosing and modest IOP reduction.

Side-effects

- Minimal irritation, transient blurred vision
- Metallic taste
- Periorbital dermatitis and allergic conjunctivitis
- Can worsen endothelial damage in decompensated corneas
- Transient myopia

Contraindication – Relative – pregnancy and lactation.

Beta blockers

1967 saw the introduction of Propranolol as the first beta blocker which was found to lower IOP after intravenous administration. The topical agent failed to gain popularity due to its adverse local side-effects. It was not till Timolol came in 1976 and the less effective but safer Betaxolol was approved in the 1980s that betablockers became the leading Antiglaucoma agents and revolutionized glaucoma pharmacology becoming the first line agents till it was finally dethroned by prostaglandins. However they still remain in common use as an adjunctive therapy owing to its efficacy, few ocular side-effects and cost. The main drawbacks however are the systemic side-effects.

Classification

- Non-Selective beta-blockers – Timolol maleate, Carteolol, Levobunolol
- Selective beta-blockers - Betaxolol

Mechanism of action – supresses aqueous humour formation by 30-50% by inhibiting adenylate cyclase

Side-effects

- Ocular – Tear film abnormalities, punctate epithelial erosions, allergic conjunctivitis
- Systemic
    - CVS – bradycardia, hypotension, heart failure
    - RS – bronchospasm, aggravating asthma, emphysema, bronchitis
    - CNS – sleep disorders, depression, rarely hallucination

Contraindications – Asthma, Chronic obstructive pulmonary disorder, sinus bradycardia and heart block

Prostaglandin analogues

The safest and most effective glaucoma drugs till date, this class of drugs changed the landscape of glaucoma pharmacology unlike no other

and quickly replaced beta-blockers as the first-line agent in glaucoma. While the prototype molecule latanoprost was developed at Columbia University as early as 1982, it took until 1996 to achieve an approvable formulation (Xalatan™, acquired by Pfizer from Pharmacia). Over the next decade additional prostaglandin analogues started emerging such as Alcon's Travoprost (Travatan™), Allergan's Bimatoprost (Lumigan™) and Merck's Taflurprost

Mechanism of action

Many studies have shown that prostaglandin analogues not only increase outflow facility by increasing uveoscleral pathway functionally but also by altering it structurally. (57) Prostaglandin analogues have been shown to produce extracellular matrix remodelling, widening of the intermuscular spaces along the longitudinal ciliary muscle and dissolution of collagen types I and III. (58) Latanoprost was shown to increase matrix metalloproteinase 1 activity in the non-pigmented epithelium of the cilary body which may account for the loss of extracellular matrix in the uveal tract and thus the increased uveoscleral outflow. (59)

Latanoprost 0.005% currently has become one of the most useful antiglaucoma agents due to its potency, single daily dosing and better safety profile.

Latanoprost is rapidly converted by the cornea into its acidic form which seems to be the active ingredient thus making latanoprost the pro-drug. It reaches maximum concentration in the aqueous humor 1-2 hours after instillation and has a half-life of 2-3 hours. In the blood stream, it reaches peak concentration in 5 minutes and has a half-life of 17 minutes.

Compared to timolol, which requires twice daily dosing and is less efficacious at night, once-a-day evening dose latanoprost was found to be more effective at lowering IOP. It persisted over 24 hours thus effectively flattening the diurnal curve and be efficacious throughout the night. There was however, a higher incidence of conjunctival hyperaemia but unlike timolol there was no incidence of any systemic side-effects like bradycardia or hypotension in patients on Latanoprost.(60) Latanoprost was also shown to have the best IOP-lowering effect, least systemic side-effects and very few significant local side-effects as compared to timolol, betaxolol and brimonidine. Waldock et has also shown that in patients with significant steroid dependent asthma, latanoprost had no adverse effect on the respiratory system. (61)

In patients with normal tension glaucoma, Latanoprost 0.005% was found to be the most potent ocular hypotensive agent when compared to β-blockers, α agonists and carbonic anhydrase inhibitors. (62)

Latanoprost was also shown to be effective in pigmentary glaucoma and steroid induced glaucoma. (63,64).

Other currently available PG analogues include Bimatoprost and Travoprost. Bimatoprost in some studies seem to show a slightly better IOP lowering effect as compared with Latanoprost and Travoprost thus also making it the most cost-effective in reaching target IOP. It was however associated with a higher incidence of local side-effects when compared to latanoprost. (65–68)

Travoprost, when compared with Timolol have shown to have similar IOP lowering over a 24 hour period but had greater duration of action of upto 40hours from a single dose. (69,70)

Unlike latanoprost, travoprost is more effective when used twice daily compared to once daily. However the proportional increase in side-effects limits its twice daily use. (71)

Side-effects associated with pg analogues:

Conjunctival hyperemia – prostaglandins are autocoids which cause vascular changes like vasoconstriction, vasodilatation and increased vascular permeability. The mechanism is possibly due to release of Nitric oxide. Conjunctival hyperemia was less associated with latanoprost (5-15%) than travoprost (35-50%) and bimatoprost (5-45%). As the

hyperemia is mostly minimal and reduces with time, discontinuing the drug of successful treatment in view of the hyperemia is not recommended. (72,73)

Eyelash Changes – hypertrichosis is well documented sideffect of prostaglandin analogue. Misdirected growth resulting in lash ptosis or trichiasis needing management has also been reported in some cases. This effect is also being studied among dermatologists for the treatment of alopecia. (74,75)

Induced iris darkening – an irreversible side-effect of all PGF2 alpha analogues, develops in the first year of treatment. The 2 possible mechanisms of induced iris darkening are an increase in iris stromal melanocyte numbers and increase melanogenesis or migration of iris stromal melanocytes to thicken the anterior border region. Incidence of iris hyperpigmentation after 6-12 months of therapy varies between 1-3% with travoprost, 5-10% with latanoprost and 1.1-1.5% with bimatoprost. (76–78)

Iris cysts – few cases have been reported with the use of latanoprost causing pigmented epithelial cyst formation possibly due to flow pressures caused by increased uveosleral drainage. Withdrawal of the drug is also shown to cause reversal of the cysts without any recurrence. (79)

Periocular skin pigmentation – long term topical PG analogues have been associated with darkening of the skin of the lids or other sites around the eyes. The mechanism, though still unclear, is possibly due to the prostanoid effects on melanogenesis and melanin production. In case of bimatoprost, it is due to contact dermatitis. The change however is reversible unlike the iris hyperpigmentation. (80–83)

Breakdown of the blood-aqueous barrier – due to PG analogue use has been linked to recurrence of uveitis in susceptible individuals and cystoid macular edema especially when there is a coexisting disruption of the posterior lens capsule which allows the inflammatory mediators to reach the macula especially after cataract extraction or even YAG capsulotomy. (84,85)

Reactivation of Herpes simplex keratitis – occasional cases of reactivation of latent herpes keratitis have been reported following the use of Pg analogues in the form of dendrites, pseudodendrites and keratouveitis. (86)

Surgical management

When compared to medical therapy, surgical management is more likely to control IOP and maintain it for a longer duration. Though the visual function may be better preserved, the visual acuity may be affected

earlier as compared to medical management due to cataract formation. (87) Being less dependent on medications, the quality of life may be better and the factor of compliance is not much of significant concern. Moreover in the long run, provided there are no complications and the benefits remain, the cost of a one-time surgery may be less than the cost of using topical medications. (88,89)

However being an irreversible treatment option with a significant risk of complication and adverse sequelae, it is understandable why trial with primary medical management is generally preferred over primary surgery

Trabeculectomy

Modern trabeculectomy, popularised by Cairns in the 1960s quickly replaced the full-thickness surgery due to lesser complications and better success rates which improved even further with antimetabolites, collagen implants, releasable sutures, laser-suture-lysis and Anti-VEGFs. (90)

Trabeculectomy, a partial-thickness filtration surgery, is currently the first choice for medically intractable glaucoma. Surgery is generally indicated when there is no internal flow block and IOP remains too high despite maximally tolerated medical therapy. The success rate of modern

trabeculectomy in experienced hands is estimated between 60 and 100%, depending on patient selection, definition of success and length of follow-up. (91)

Cataract and Glaucoma

Glaucoma being a disease of the elderly often coexists with cataract and each condition can influence management of the other. In developing countries, glaucoma is often detected at an advanced stage when the patient presents with cataract. In areas with poor health care and accessibility, patients can present late with phacolytic or phacomorphic glaucoma. Progressive lens change can mimic the functional changes seen in glaucoma such as visual field loss and reduced visual acuity, the anatomical changes such as narrow angles and hinder optic disc visualization making diagnosis difficult. Alternatively long term Antiglaucoma medications (eg. anticholinesterases) or even prior glaucoma surgery can accelerate cataract formation. (92)

Hence the importance of considering both these diseases while planning the treatment of one.

While considering patients with glaucoma and visually significant cataract there are 3 choices

1. Cataract surgery first and tackle the glaucoma aspect later.
2. Glaucoma filtering surgery first and tackle the cataract aspect later after full healing.
3. A combined procedure with cataract extraction, IOL implantation along with a filtration surgery in one sitting.

Cataract surgery alone causes a long term pressure reduction of 2-4 mmHg which may be acceptable in a patient with minimal disc and field change and well controlled IOP on minimal medical therapy. However it is not sufficient for adequate IOP control in all cases thus requiring same or increased medical management after 1 year in a great majority of patients. (93,94)

In the presence of early cataract and medically refractory glaucoma, a good filtration procedure is a good choice. However the effect the subsequent cataract surgery has on the prior successful filtering surgery needs to be addressed. Most studies have shown that pre-existing filtering surgery can get compromised due to the subsequent cataract extraction with a bleb failure rate up to 30-40% possible due to the inflammation following the IOL surgery. Even temporally performed phacoemulsification has been reported to cause some adverse effect on

the pre-existing glaucoma control such as postoperative increased IOP, need for antiglaucoma medications or changes in bleb morphology. Thus it is possible to lose some IOP control from a prior filtering surgery if a cataract surgery is performed at a later date. (95–97)

The advantages of a combined surgery are as follows

1. Better long term IOP control than cataract surgery alone.
2. Surgery performed in a single sitting.
3. Excellent visual acuity following the surgery in a majority of the patients (in absence of retinal pathology)

Studies comparing ECCE + IOL + trabeculectomy with phacoemulsification + IOL + trabeculectomy, have shown the latter to be superior in most cases with reliable results such as better visual acuity, lower IOPs with fewer medications, fewer postop complications and morphologically better looking blebs. This was attributed to the smaller incisions needed for surgery. (59,97–100)

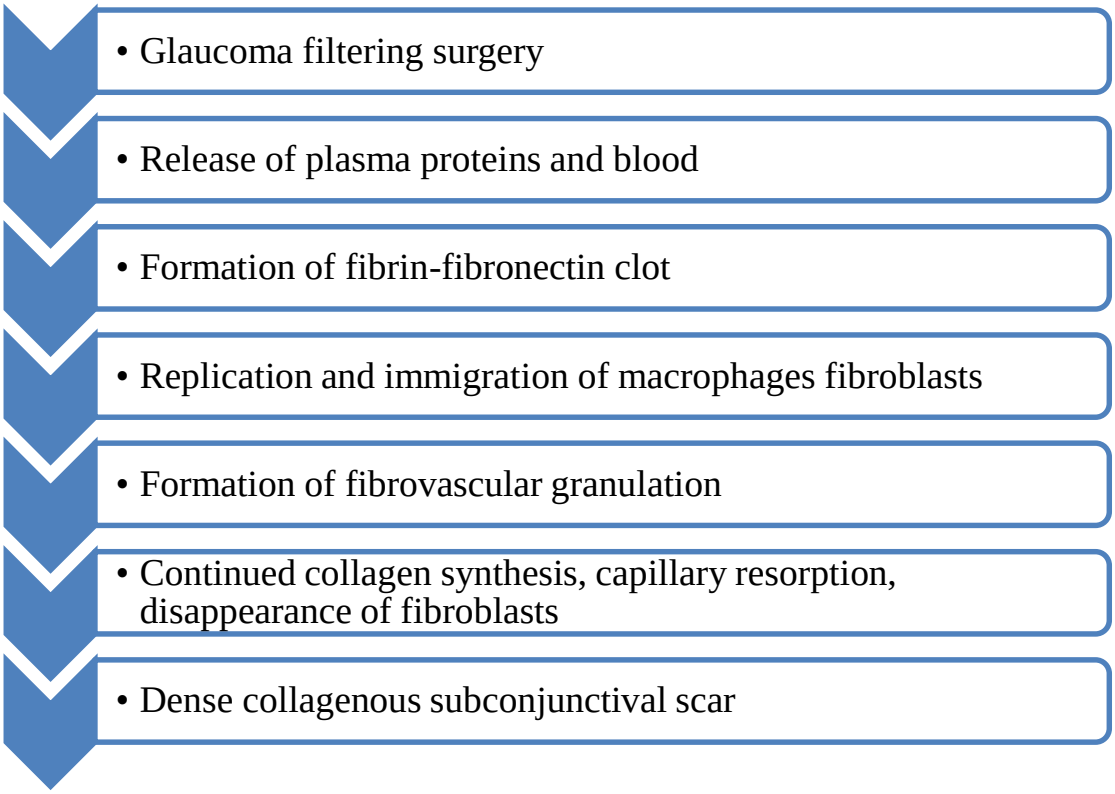
Addition of antimetabolites like MMC to Phacoemulsification + IOL + trabeculectomy have improved the outcomes of surgery even further with consistently low IOPs, good visual outcomes, large and functional blebs.

Characteristics of A filtering bleb

The appearance of filtering bleb is an important factor in evaluating the outcome of glaucoma filtering surgery. (101)Successful outcome can be anticipated when there is minimal engorgement of conjunctival vessel during first week. By second and third week, bleb becomes more localized and by the end of first month, a well-established and moderately diffuse bleb is formed. The bleb will become gradually less hyperemic, well established with microcystic vesicles on conjunctival surface in around three months. Bleb failure or subconjunctival fibrosis is the most common cause of filtering surgery failure.

Wound healing after Glaucoma surgery

The series of events from surgical trauma to formation of mature scar are



The surgically fashioned fistula between the anterior chamber and the sub-conjunctival space may fail to drain the aqueous humor successfully because of

- Closure of the fistula with granulation tissue in the immediate post-op period
- Encapsulated bleb or Tenon's capsule cyst which forms a thick walled cavity around the loculated aqueous preventing drainage during the first few weeks after surgery.
- Sub-conjunctival fibrosis and flattening of the bleb months or years after filtering surgery

Complications of filtering surgery

Intraoperative complications

1. Button holing of the conjunctiva – avoided by meticulous handling and use of non-toothed forceps. It is more common with re-surgery and presence of adhesions. They are difficult to manage and can result in hypotony, shallow anterior chamber or scarring of the bleb. Direct repair can be done using purse-string suture or mattress sutures using 10-0 Nylon. If repair is not possible, a new surgical can site can be chosen.

2. Flap-related complications – flap tears, premature entries and amputations can occur if the scleral dissection is done in the incorrect plane. This is more common in buphthalmic or myopic eyes thus requiring extra care in these conditions. Flap tears can be managed by suturing to the anterior limbal tissue and taking a new flap in a deeper plane. Total flap amputations however may need donor scleral flaps.

3. Hemorrhage – can occur subconjunctivally or from sclera during dissection which can affect visualization and can predispose to bleb failure. Hyphema can occur during iridectomy which may need drainage via paracentesis if large. Suprachoroidal haemorrhage though rare is a dreaded complication of filtering surgery and especially associated with higher preoperative IOPs, longer axial length and in patients with higher episcleral venous pressure. The risks are also significantly higher among aphakics, vitrectomised eyes, patients with congenital glaucoma and those who are on anticoagulants. This can be prevented in the high-risk groups by using pre-op hyperosmotic agents to reduce the IOP or releasing the aqueous gradually via paracentesis. If suspected, the flap should be immediately closed and sclerotomies performed in select cases after 2-3 weeks to drain the fluid.

4. Expulsive haemorrhage – due to sudden lowering of intraocular pressure leading to bleeding from suprachoroidal vessels. Prevented

by adequate lowering of IOP prior to surgery and controlled decompression of the globe intraoperatively via paracentesis.

Early Postoperative complications

1. High IOP and Deep chamber can be due to obstructed flow at the sclerotomy site due to tight sutures which can be released or lysed using laser or blood/fibrin/iris/vitreous plugging the ostium the latter two requiring intervention. Persistently flat bleb with a raised IOP can be due to scarring at the episceral surface which can be managed using subconjunctival injections of 5FU with or without needling.

2. High IOP with a shallow chamber can be due to pupillary block resulting in iris bombe or aqueous misdirection. Aqueous misdirection or malignant glaucoma can be managed medically by cycloplegics and aqueous suppressants. No response to medical treatment indicates need for intervention by disrupting the anterior hyaloid face using Nd-YAG laser or pars plana vitrectomy.

3. Delayed Suprachoroidal haemorrhage characterised by sudden onset pain, nausea and loss of vision. Clinical features include, flat AC, loss of red reflex and dome shaped choroidal elevations. USG- B scan can demonstrate blood in the suprachoroidal space. Management of small

haemorrhages can be conservative with topical and systemic steroids while larger ones require drainage.

4. Wound leaks should be thought of if there is hypotony without a visible bleb and localised with the Seidel's test. If antimetabolites were used intraoperatively even small leaks may need surgical closure else conservative treatment with patching, aqueous suppressants, cycloplegics and topical antibiotics like gentamycin or tobramycin (known to induce scarring) may suffice especially if the leak is small with a well-formed bleb and anterior chamber.

5. Choroidal detachment is usually caused by hypotony. A vicious cycle can set in as the detachments further reduce aqueous flow. Management is mostly conservative with topical steroid and cycloplegics. Choroidal drainage is indicated only in kissing choroids and refractory choroidal detachment.

Late postop complication

1. Chronic hypotony is said to occur if the hypotony lasts for more than 3 months and is associated with drop in visual acuity and hypotony maculopathy characterised by choroidal folds with retinal striae without edema. Risk factors being young age and myopia. Treatment options that can be attempted prior to surgical revision with scleral

patch graft include soft contact lenes, cryotherapy to reduce bleb size, autologous blood injection and argon laser to the bleb.

2. Bleb leak usually seen in thin walled blebs following anti-metabolite application during surgery. Detected using Seidels test, if present, these can be managed with aqueous suppressants, antibiotics, patching or soft contact lenses. Risk of endophthalmitis warrants the need for careful monitoring of these cases. Leaks that do not respond to conservative management and large leaks need alternative options like – cyanoacrylate glue, fibrin tissue glue, autologous blood injection and surgical revision.

3. Failed or failing bleb – mainly attributed to subconjunctival fibrosis. Formation of an encapsulated bleb prevents filtration of aqueous out of the bleb. Bleb failure can be addressed by needling with antimetabolite injection. Repeat surgery may be needed when other measures fail.

4. Bleb related infections, blebitis and Endophthalmitis – common risk factors are thin-walled blebs seen with antimetabolite use, hypotony, leaking bleb, diabetes and inferior limbal blebs. Onset of infection can range from few days to up to 20 years following filtration surgery. Topical as well as systemic antibiotics are needed along with intravitreal injections in case of endophthalmitis.

REVIEW OF LITERATURE

The first line therapy for glaucoma continues to be Antiglaucoma medications and there is a high possibility that most individuals with glaucoma will be treated for prolonged periods of time with topical agents. It is thus necessary to assess the effect of these medications on the external and internal structures of the eye and what that translates to in subsequent filtration surgery.

Since conjunctival scarring was known to be the most common cause of bleb failure following trabeculectomy and patients who underwent early filtration surgery had better surgical outcomes when compared with those who were previously on topical medications, many ophthalmologists believed the local side effects of the drugs to be a causative factor. (21–23) Studies have been carried out since way back in 1989, in order to determine the local side-effects of Antiglaucoma medications. Sherwood et al conducted conjunctival and tenons capsule biopsies in 2 patient groups; one which underwent primary surgery for glaucoma and the other which received at least two types of topical Antiglaucoma medication for a minimum period of 1 year prior to surgery. They found a significant decrease in the number of goblet cells , increase in hyaline bodies and nonepithelial cells in the epithelium, an increase in macrophages, fibroblasts and mast cells in the substantia

propria and tenons capsule of multi-treatment group compared to the primary surgery group. This suggested that exhaustive medical therapy prior to surgery increases the number of tissue inflammatory cells and thus enhance the risk of external bleb scarring post filtration surgery. The limitations however were that the number of patients included in the study were far too low to note any differences among the different types of Antiglaucoma agents(22).

Longstaff et al in 1990 demonstrated that long term topical Antiglaucoma medications prior to surgery was a significant risk factor for surgical failure.(23) The same year Lavin et al compared the surgical outcomes among 2 groups of patients who underwent trabeculectomy - 1 group with a history of medical treatment for more than a year and the other group for less than 8 weeks. This unmasked retrospective clinical study provided significant proof that long term topical Antiglaucoma medications can adversely affect surgical outcomes. However the duration of treatment was not strictly documented.(21) Two years later Schwab et al had reported significant foreshortening of the inferior fornix secondary to conjunctival fibrosis further suggesting the possibility that long term medications increases the risk of surgical failure.(102)

Broadway et al first published a review article in 1993 on the conjunctival changes caused by topical Antiglaucoma medication in

which he suggested the conjunctival reaction to follow a spectrum from severe clinical disease to total tolerance. (Table 3.1) (56) The mechanisms that fall within this spectrum (Table 3.2) are many, with pseudopemphigoid being the most severe. Drugs like beta-blockers and pilocarpine have been reported to cause pseudopemphigoid though the numbers are relatively less. Most patients, he suggested, however only fall into the middle of the spectrum with subtle and subclinical clinical effects which are more pronounced with topical sympathomimetics and miotics compared to betablockers. Long term beta-blockers have been shown to cause conjunctival changes like epithelial oedema, reduced goblet cells and secretory epithelial cells.

Table 3.1. Conjunctival changes following topical medications

Severe Clinical Disease	**Mild Clinical Disease**	**Subclinical effect**	**Total tolerance**
Obvious signs and symptoms	Subtle signs and symptoms	No signs/symptoms but cellular and ultrastructural changes	No signs/symptoms, cellular /ultrastructural changes

Table 3.2. The mechanism by which conjunctiva reacts to drugs

1. Cicatrising conjunctivitis
2. Anaphylactoid (allergic) acute or chronic conjunctivitis (type I hypersensitivity)
3. Allergic contact conjunctivitis (type IV hypersensitivity)
4. Non-specific irritative/toxic conjunctivitis (non-immunological irritation to factors such as pH, tonicity, contamination)
5. Specific irritative/toxic conjunctivitis (characterised by the formation of lymphoid follicles)
6. Cumulative/deposition/dyschromia (for example, adrenochrome deposition with sympathomimetics)
7. Microbial imbalance and secondary conjunctivitis (delayed allergic response, ? type IV hypersensitivity)
8. Non-specific irritation (in the absence of clinical signs)
9. Subclinical cellular and
10. Ultra-structural changes
11. Total tolerance

Broadway et al later followed with two papers in 1994 on adverse effects of topical Antiglaucoma medications. The first, focused on the conjunctival cell profile and the second on the outcome of filtration surgery. Subsequently in 1996 he also studied the effect of topical

corticosteroid in reversal of the conjunctival changes induced by topical antiglaucoma medications. In their first study, which evaluated the conjunctival changes induced by Antiglaucoma medications, they found irrespective of type of drug, administration of topical medications for more than 3 years induced significant changes which were worse with multidrug therapy.(103)

Broadway et al in their subsequent study proved that long term topical combination therapy could be significant risk factor for failure of filtration surgery. They reported surgical failure being associated with changes in all 3 layers of the conjunctiva such as significantly more pale cells ($P<0.01$), macrophages and lymphocytes in the epithelium, fibroblasts ($P<0.05$) and macrophages ($P<0.05$) in the superficial substantia propria; and both macrophages and lymphocytes in the deep substantia propria ($P<0.01$).(19)

His follow-up study in 1996 on the effect of reversal of conjunctival changes was able to show not only a histologically significant reduction in conjunctival cellularity but also some improvement in the success rate of trabeculectomy when the patients were started on a weak topical corticosteroid and asked to discontinue the sympathomimetic 1 month prior to surgery. Patients with advanced glaucomatous field loss nearing fixation however were and should be

exempted from this regimen due to the theoretical risk of rise in IOP.(104)

Hong et al (2006) concluded that long term Antiglaucoma medications can alter the conjunctival surface by causing significant squamous metaplasia and thus adversely affect the outcome of glaucoma surgery. In this study the impression cytology scores according to Nelsons method were found to be higher among those on combination therapy as compared to single drug therapy though there was no significant difference among the different types of Antiglaucoma agents.(20,105)

Ocular surface disease and Glaucoma

Ocular surface disease is frequently encountered in patients with glaucoma especially those on long term topical agents. Fraunfelder et al (2006) reported a significantly higher incidence of corneal toxicities among patients on Antiglaucoma agents, when compared to those on topical aminoglycosides for bacterial keratitis. The pathophysiology was possibly through the reduction of tear-film stability.(106) Similar reports were also given by Baffa et al who suggested the preservative present in most Antiglaucoma medications could be the reason behind these changes especially BAK. (107)

In a baffling and surprising twist, our literature search also revealed a retrospective study by Johnson et al (1994) which suggested that preoperative use of topical medications did not influence the outcome of glaucoma surgery.(29) Unfortunately the full article was not accessible.

Prostaglandin analogues

Conjunctival hyperaemia as a side-effect is reported commonly following topical prostaglandin analogue therapy , over twice of that seen with timolol.(108) Our literature search revealed a meta analysis by Honrubia et al in 2008 and one by Eyawo et al in 2009 both of which showed higher incidence of hyperemia following topical Bimatoprost and travoprost as compared to Latanoprost.(73,109) Hyperaemia caused by prostaglandin analogues is of concern for ophthalmologists as it can lead to surgical failure as well as poor compliance due to the poor cosmesis. The cosmetic change is also of concern as it was attributed by nearly two-third of patients in another study by Friedman et al as a cause for non-compliance to treatment.(110) However there is no proven evidence stating that hyperemia alone decreases surgical success rates.

The incidence of subclinical inflammation is of significant concern as the status of the conjunctival and subconjunctival tissue is an important factor for surgical success. Guenoun et al who studied the action of prostaglandin analogues in vitro conjunctiva-derived cells suggested the

toxicity is more induced by the preservative than the medication itself. He also found a possible protective effect of prostaglandin analogues against BAK toxicity as he found reduced inflammatory markers even with higher BAK concentrations.(111) Conversely, Uusitalo et al reported HLA-DR expression, marker of inflammation, even among patients using preservative free prostaglandin analogues.(112) Furtado et al compared the conjunctival expression of HLA-DR, in eyes treated with topical prostaglandin analogues versus eyes treated with other drugs and found no significant increase in HLA-DR among the group on topical prostaglandin analogues. Interestingly in a previous study by the same group which studied impression cytology specimens, the expression of HLA-DR was higher among patients using prostaglandin analogues even without any clinical signs of inflammation which is frequent in early stage of treatment. (113,114) Russ et al compared the effects of prostaglandin analogues and timolol maleate in the rabbit conjunctiva and demonstrated that timolol induced more severe changes as compared to prostaglandin analogues which could be the consequence of enhanced fibroblast activity. They also reported increased goblet cell count in patients treated with prostaglandin analogues, a change not seen with timolol.(115) Terai et al who compared the effect of timolol and latanoprost on the human conjunctiva found the latanoprost treated group to have lesser inflammatory reaction than the timolol group. The study

also found an up regulation of CD68 antibodies, an indicator for acute and chronic inflammation, among the timolol group and concluded that latanoprost therapy might have a more favourable effect on the outcome of trabeculectomy. (116) Similar conclusions were also made by Pisella et al who compared in vitro and in vivo effects and showed while unpreserved formulations were definitely better, preserved latanoprost caused less toxicity than preserved timolol.(117)

Perez-Roca et al (2015) recently studied the effects of prostaglandin analogues on primary cultures of human conjunctival stromal cells and reported cell damage with all four prostaglandin analogues, latanoprost, bimatoprost, travoprost and tafluprost. Among the 4 formulations, tafluprost was less toxic although they did acknowledge the fact that this was the only formulation which did not contain BAK as a preservative. (118) The reduced toxicity of preservative free tafluprost compared to commercially available Latanoprost preserved with BAK was previously reported by Liang et al, back in 2008, on rabbit cornea and conjunctiva.(119)

Benzalkonium chloride

Used as a preservative in most glaucoma medications, Benzalkonium chloride (BAK) had been implicated as one of the major causes of conjunctival inflammation in eyes undergoing long term

treatment.(120) This quarternary ammonium detergent exerts antibacterial activity by causing non selective cytoplasmic membrane lysis and protein denaturation making it ideal to prevent bacterial contamination of traditionally designed multidose ophthalmic solution containers.(120) The down-side however has been the cytotoxic effects on the ocular surface which can cause conjunctival metaplasia and tear film breakdown.(19,121–123) Badouin C reported 24 out of 26 patients receiving treatment with two or more BAK preserved drugs for at least 1 year had abnormal inflammatory markers, fibroblastic markers or both. (124) Thus it wasn't a surprise when prolonged use of preserved antiglaucoma agents was associated with increased risk of early trabeculectomy failure owing to the subclinical conjunctival inflammation.(19) The PESO Study was able to show a dose response curve with respect to the amount of preoperative BAK exposure and proved that increased amount of preserved drops used per day increases the risk for early qualified failure. With each additional drop containing BAK, the study showed an increase in risk of failure by a factor of 1.21 making BAK the most likely etiological agent behind failure of filtration surgery. (125)

Alternatives to BAK

Three new, less toxic preservatives currently available are Purite, a stabilized oxychloro complex, Sofzia, a buffer system containing boric acid, propylene glycol, sorbitol, and zinc chloride, and Polyquad (polyquaternium- 1), a polycationic polymer previously used in personal care products and for contact lens care. Studies have shown, inflammatory cells and damage scores with purite based formulations to be significantly less than formulations containing BAK.(126). Sofzia or polyquad have also been shown to be safer than BAK.(127,128).

PART – II

MATERIALS AND METHODS

Objective

To evaluate the effects of prostaglandin analogues on surgical outcomes of glaucoma filtration surgery

- To determine the effect of topical prostaglandin analogues as compared to other antiglaucoma agents on the results of glaucoma filtration surgery.
- To determine the effects of prostaglandin analogues as compared with other Antiglaucoma agents on the cell population profile of the conjunctiva and to relate any differences to the outcome of glaucoma filtration surgery.

Materials and Methods

Study setting – Aravind Eye Hospital and PG Institute of Ophthalmology, Madurai

Study design – Cohort study

Study population – All diagnosed cases of POAG/PXFG undergoing Glaucoma triple procedure from Jan 2016 to December 2016 who have been on topical Antiglaucoma medications for a minimum period of 3 months

Duration of study – I year recruitment and 6 months follow-up

Selection criteria – patients >45 years age suffering from glaucoma (POAG or PXFG) on topical medications for a minimum of 3 months duration undergoing glaucoma triple procedure.

Exclusion criteria

- Patients suffering from ocular or systemic inflammatory diseases
- Patients on long term topical steroid medications
- Previous history of eye surgeries
- Secondary glaucoma

Statistical analysis

The information collected regarding all the selected cases were recorded in a Master Chart in Microsoft Excel sheet. Data analysis was done with the help of computer using the software Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 22.0 for Windows).

Quantitative variables were expressed as mean and standard deviation. Student’s unpaired test was used to test the significance of difference between quantitative variables and Yate’s and Fisher’s chi square tests for qualitative variables. A 'p' value less than 0.05 denotes significant relationship.

Sample size calculation

The sample size of 116 (58 in each arm) patients was calculated to be included in the study to prove the difference of surgical success between prostaglandin and non-prostaglandin groups, with assumed percentage of surgical success in prostaglandin 50% and in non-prostaglandin 75%, and 5% level of significance, 80% power.

Methodology

After obtaining permission from the institutional ethics committee consenting patients were selected based on the inclusion and exclusion criteria.

Informed consent forms were administered to the patients who satisfy the inclusion and exclusion criteria prior to the surgery.

Information was taken as per the proforma preoperatively. Patient was evaluated postoperatively for signs of bleb failure and followed up for upto 6 months.

Consenting patients who satisfy the selection criteria were subjected to a conjunctival biopsy at the time of surgery.

A 2mm x 2mm superior bulbar conjunctival biopsy was taken from the edge of the conjunctival flap at the time of filtration surgery with minimal crush damage and sent for histopathological examination after

preserving in formalin. Biopsy specimens were taken from the same conjunctival region to reduce the regional differences in cellularity. All biopsy specimens were taken before the application of antimetabolites.

The samples were evaluated by a masked observer, after processing and staining, for number of goblet cells, intraepithelial and subepithelial lymphocytes, mast cells and plasma cells under light microscope. The average of 3 high power fields was taken for cell counts. For each specimen, the numbers of goblet cells and lymphocytes were counted in the epithelial layer and the numbers of lymphocytes, plasma cells and mast cells were counted in the subepithelial layer and substantia propria. Cell counting and identification were established by rigid criteria. Cells were counted only when both nuclear and cytoplasmic morphologic features made clear identification of cell type possible.

Patients were evaluated during the subsequent follow-up visits and categorised based on the success criteria.

Surgical technique

A superior fornix-based conjunctival flap was dissected. Using gentle bipolar cautery hemostasis was achieved. Mitomycin C (MMC) 0.4mg/ml was soaked onto 3 fragments of weck-cell sponge and these were inserted into the subconjunctival space as posteriorly as possible.

After 2 minutes sponges were removed and the area was irrigated with 20ml balanced salt solution to wash out the residual MMC. A 4 × 4 mm triangular or quadrangular scleral flap was dissected upto the clear cornea. Phaco was performed via a temporal corneal section and intraocular lens inserted. A window opening is created under the flap with a Kelly's punch to remove a portion of the sclera, Schlemm's canal and the trabecular meshwork to enter the anterior chamber. The scleral flap closure was performed with fixed or releasable 10-0 nylon sutures depending upon the surgeon's judgement. Balanced salt solution was irrigated through the paracentesis to ensure filtration. Water tight conjunctival suturing was performed with 8-0 vicryl wing sutures. More balanced salt solution was irrigated through the paracentesis to form the anterior chamber. Intracameral Moxifloxacin 0.1mg was injected, atropine 1% drops were applied and eye was patched and shielded.

Post-operative care and evaluation

A standard post-operative regimen of topical antibiotic steroid eye drops (Gatifloxacin 0.3% w/v with Prednisolone acetate IP 1.0%) for first 90 days (in tapering doses every week) was followed in both the groups along with Homatropine eye drops (2 times a day for 1 month). Glaucoma medications for the non-operated eye were continued.

Post-operatively, patients of both groups were reviewed on

- 1st day
- 15days
- 1 month
- 3 months
- 6 months

In each visit the parameters assessed were

- Best corrected visual acuity using Snellen's Chart at 6 meters
- IOP using Goldmann Applanation Tonometer (except in Post-operative day 1)
- Number of anti-glaucoma medications used
- Complications and interventions

Complications were defined as follows- shallow anterior chamber, hyphema, choroidal effusion, persistant leakage, hypotony (IOP<5mmhg), macular edema, encapsulated bleb, suprachoroidal haemorrhage, blebitis and endophthalmitis.

Releasable suture removal, laser suture-lysis and bleb needling was considered as a part of normal post-operative care and therefore not considered as a re-surgery or failure. Bleb revision or repeat

trabeculectomy or use of Glaucoma drainage device were considered as re-surgery/failure.(129)

Surgical outcomes according to guidelines given by the World Glaucoma Association.(129)

- Complete success - final recorded IOP <=21 mmHg and >6 mmHg without anti glaucoma medications or bleb needling after surgery, no postoperative laser treatment (except for YAG capsulotomy or argon laser suture lysis) and no further incisional surgery for control of IOP.
- Qualified success - IOP <=21 mmHg and >6 mmHg with one or more anti glaucoma medications or bleb needling and no postoperative laser treatment (except for YAG capsulotomy or argon laser suture lysis) and no further incisional surgery for control of IOP.
- Failure - IOP of more than 21 mmHg or less than 6 mmHg on 2 consecutive study visits
- Complete failure - loss of light perception attributable to glaucoma, or the necessity for further glaucoma surgical intervention like incisional surgery or trans-scleral diode laser treatment to control IOP

Figure 4.1. Fornix based conjunctival flap

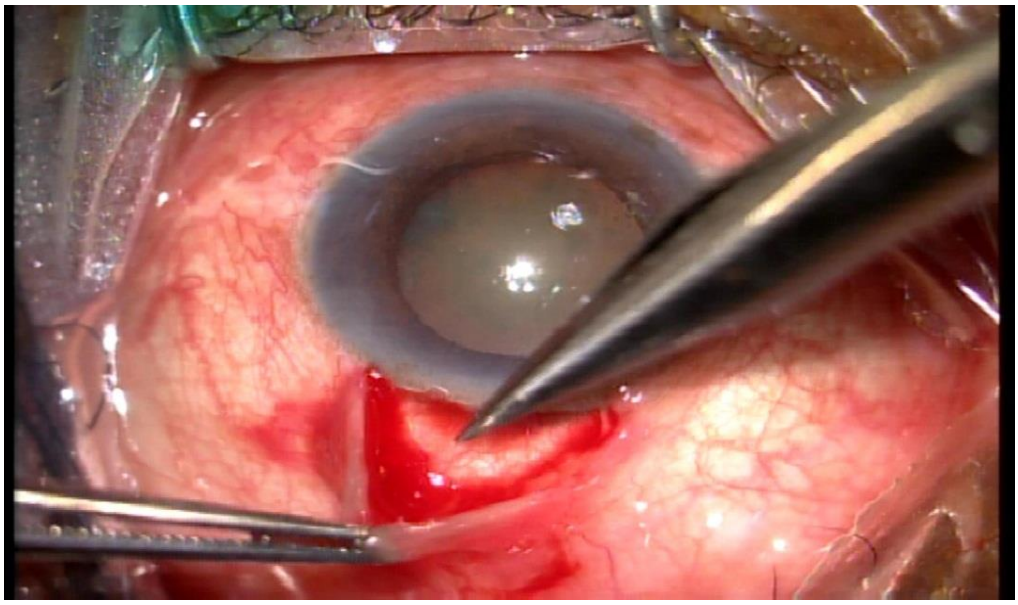


Figure 4.2. Application of MMC sponges

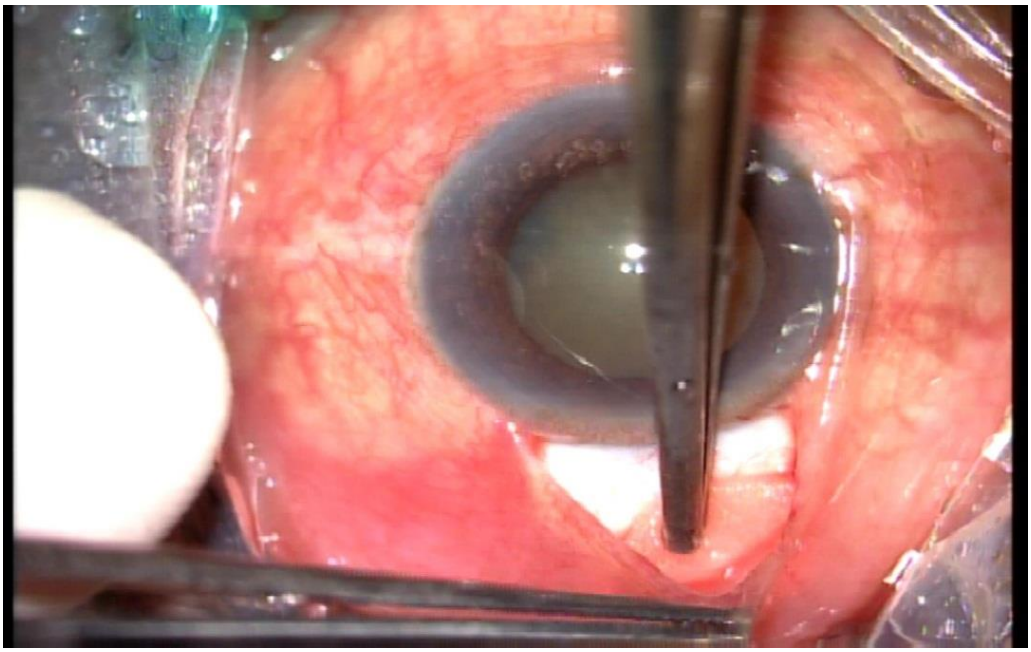


Figure 4.3. Creation of partial thickness scleral flap

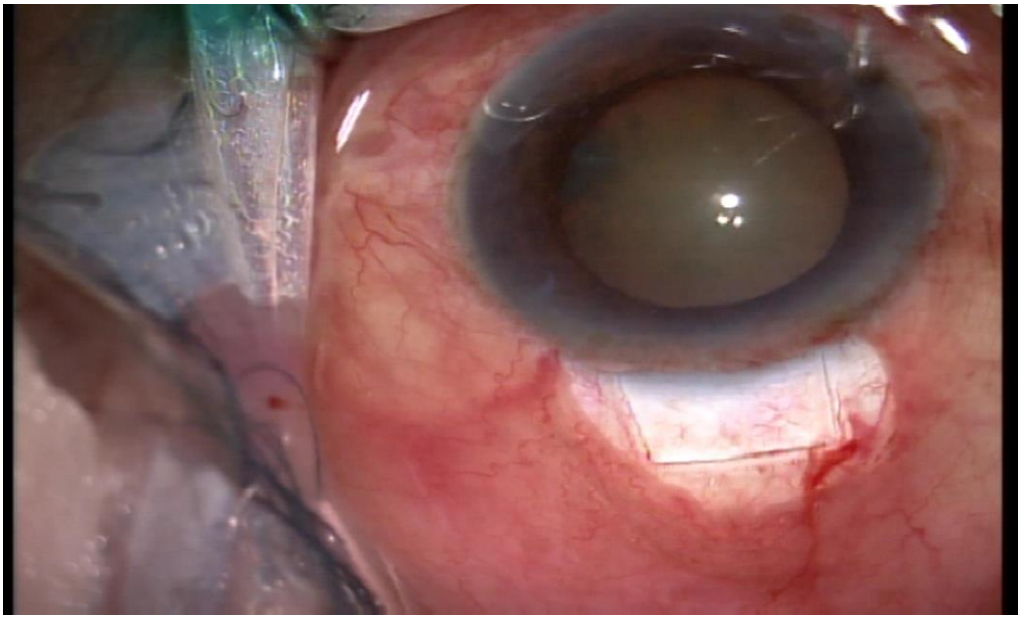


Figure 4.4. Phacoemulsification

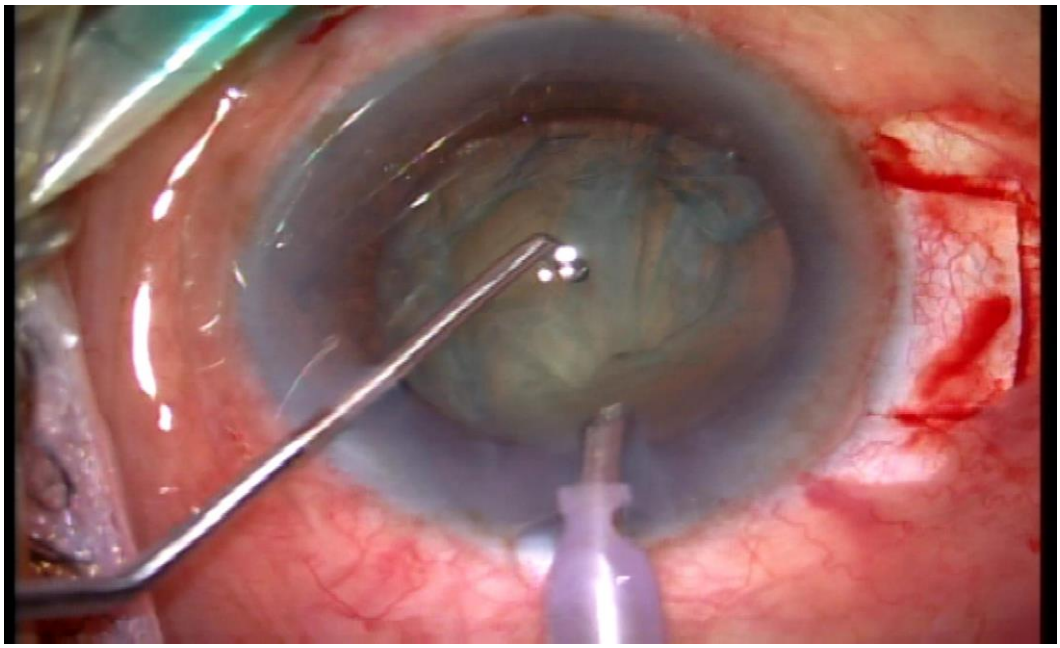


Figure 4.5. Foldable IOL placed in bag

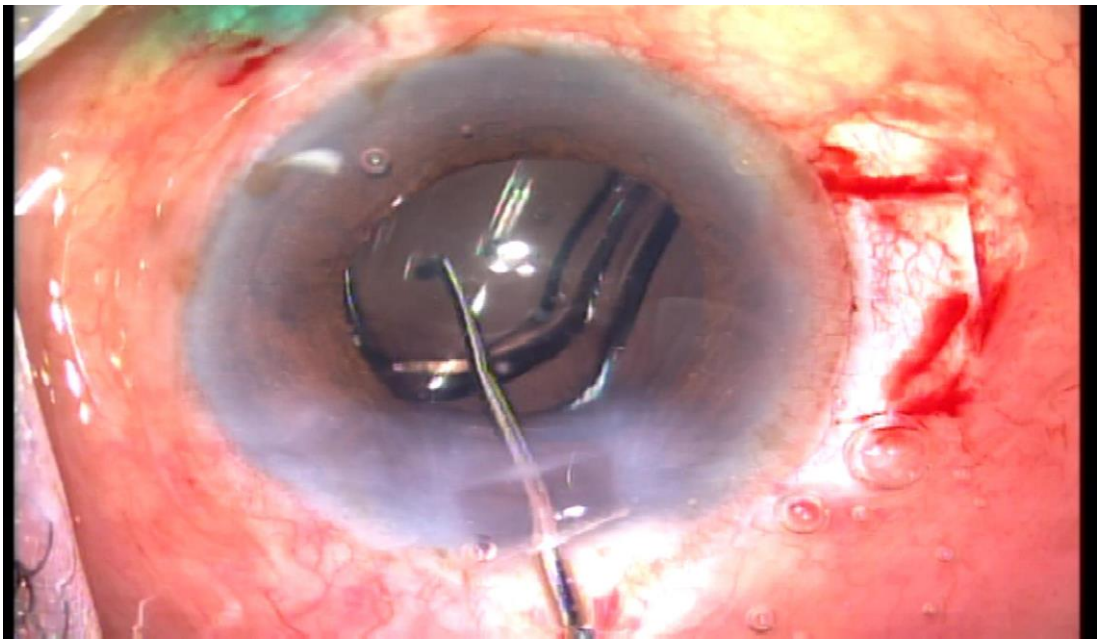


Figure 4.6. Sclerostomy using Kelly's punch

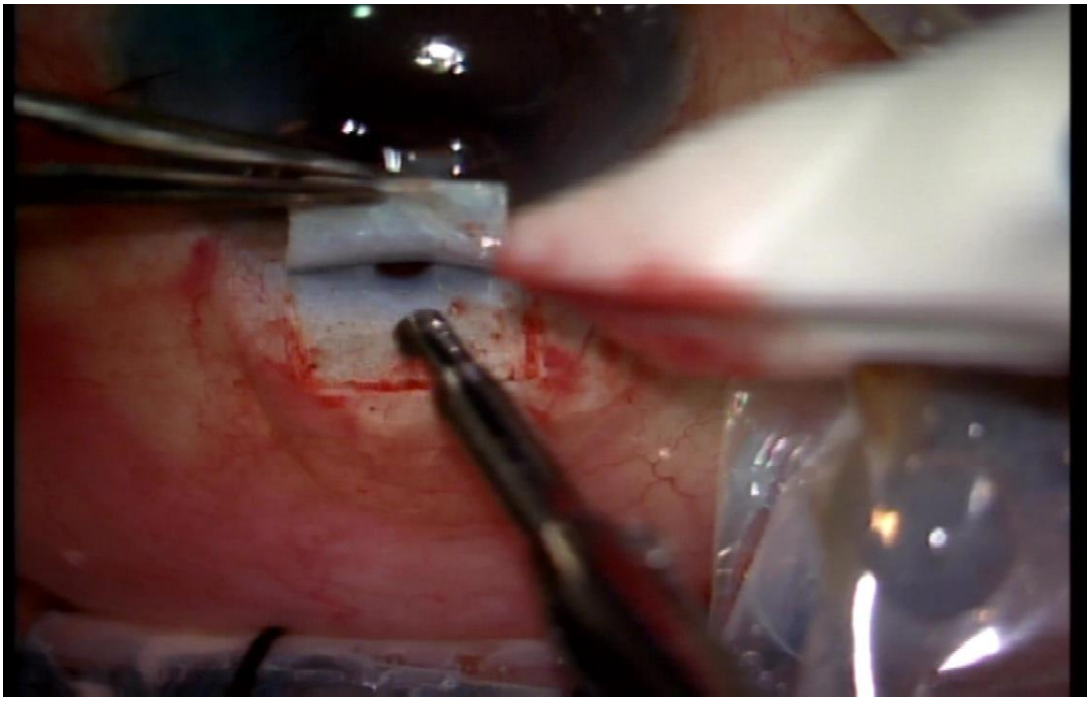


Figure 4.7. Surgical iridectomy

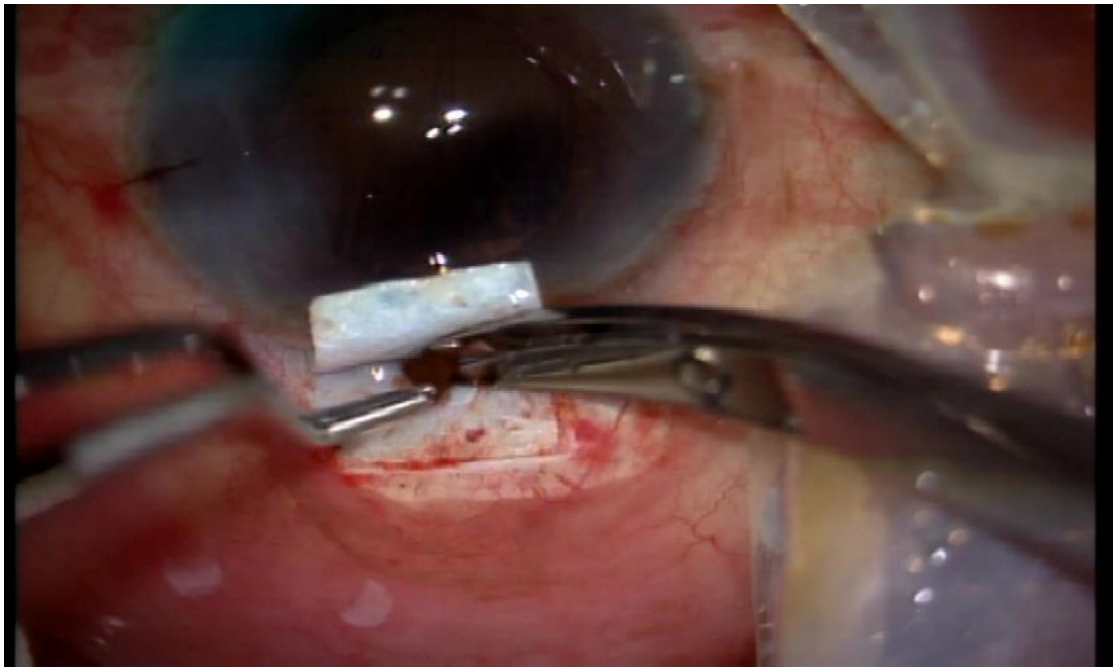


Figure 4.8. Closure of scleral flap with 10-0 Nylon sutures

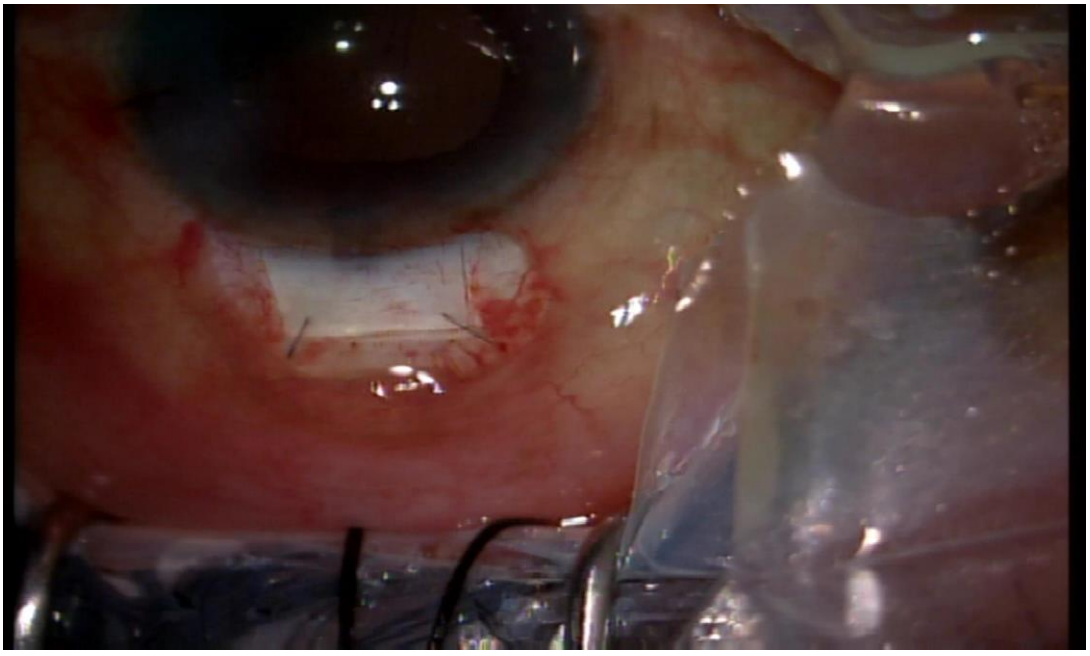


Figure 4.9. Conjunctival closure with 8-0 Vicryl sutures

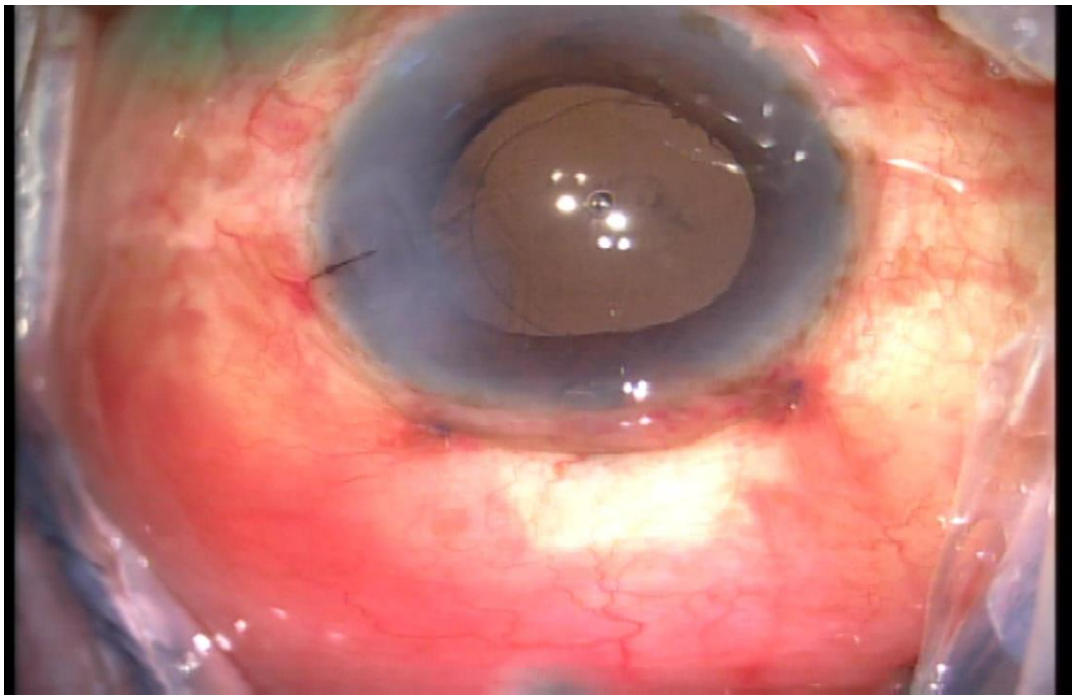


Figure 4.10. Good bleb at Postop day 1

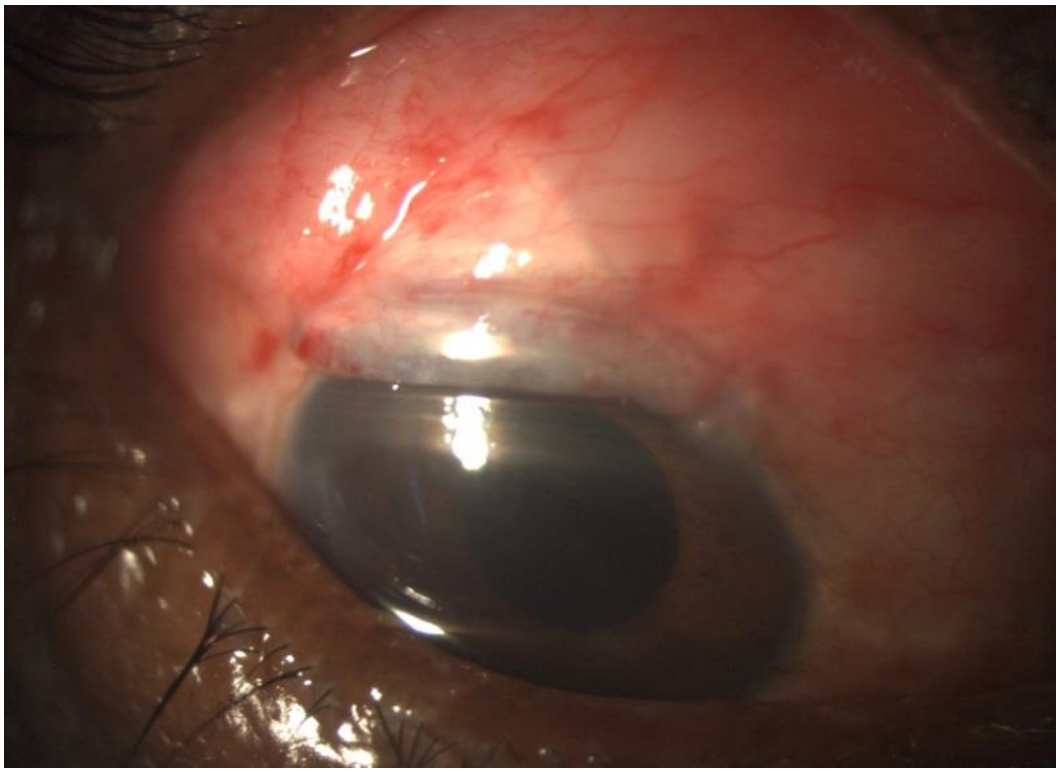
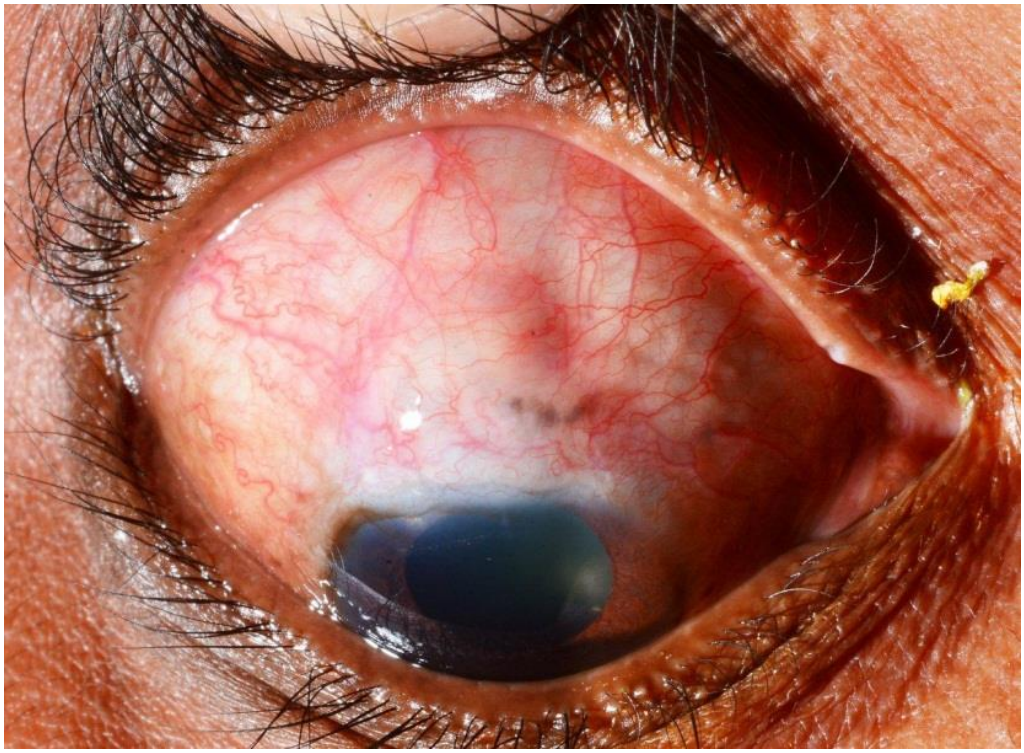


Figure 4.11. Good bleb at 2 weeks postop

Figure 4.12. Well-functioning bleb at 1 month



RESULTS

Over a one year recruitment period from January to December 2016 a total of 109 eyes of 109 patients were recruited who satisfied the inclusion and exclusion criteria. Of the total number recruited, 7 cases were lost to follow-up. The rest 102 patients were observed for a minimum period of 6 months from date of surgery for signs of bleb failure or fibrosis. The results and observations of our study has been shown in the following tables and their corresponding graphs.

Demographic details

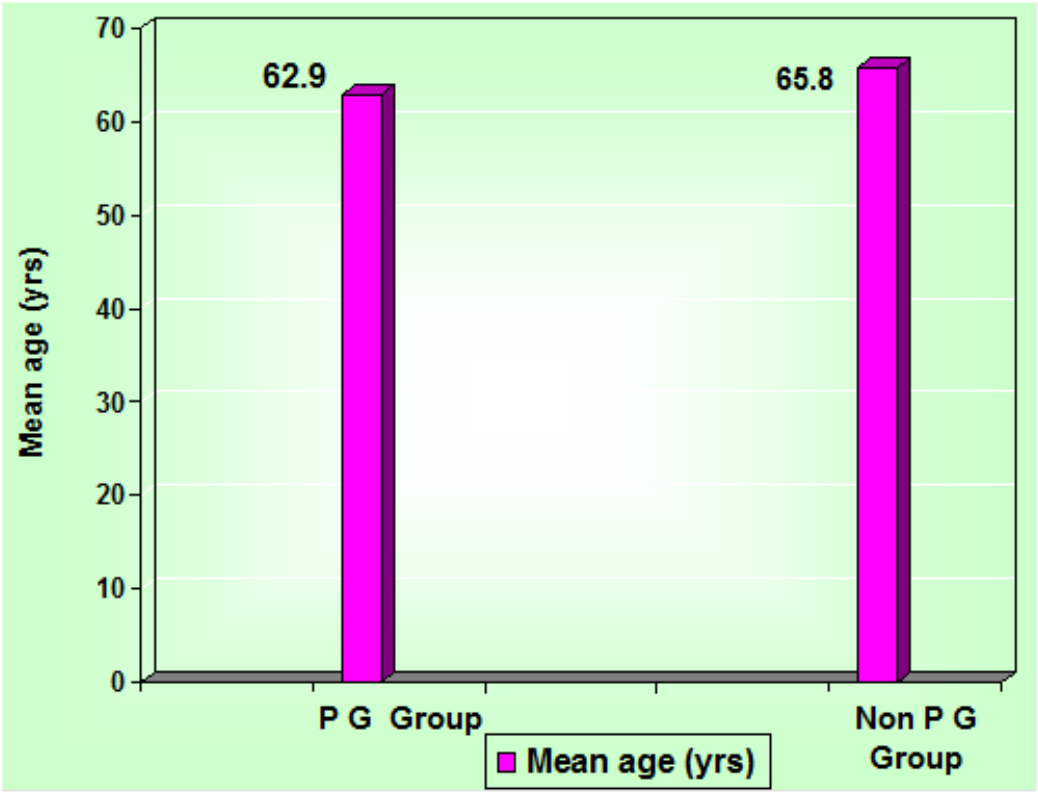
Age distribution

Most patients in our study population (47.7%) were in the 6^{th} and 7^{th} decade of life. The mean (SD) age of patients in the PG analogue group was 62.9 (7.8) years and Non PG analogue group was 65.8 (9.5) years which was not statistically significant (p – 0.096).

Table 5.1

Age distribution	PG Group		Non PG Group	
	No	%	No	%
Up to 50 yrs	3	7.1	6	9.0
51 – 60 yrs	10	23.8	13	19.4
61 – 70 yrs	25	59.5	27	40.3
71 – 80 yrs	2	4.8	16	23.9
Above 80 yrs	2	4.8	5	7.5
Total	42	100.0	67	100.0
Range	45 – 81 yrs		45 – 82 yrs	
Mean	62.9		65.8	
SD	7.8		9.5	
'p'	0.096 Not Significant			

Figure 5.1



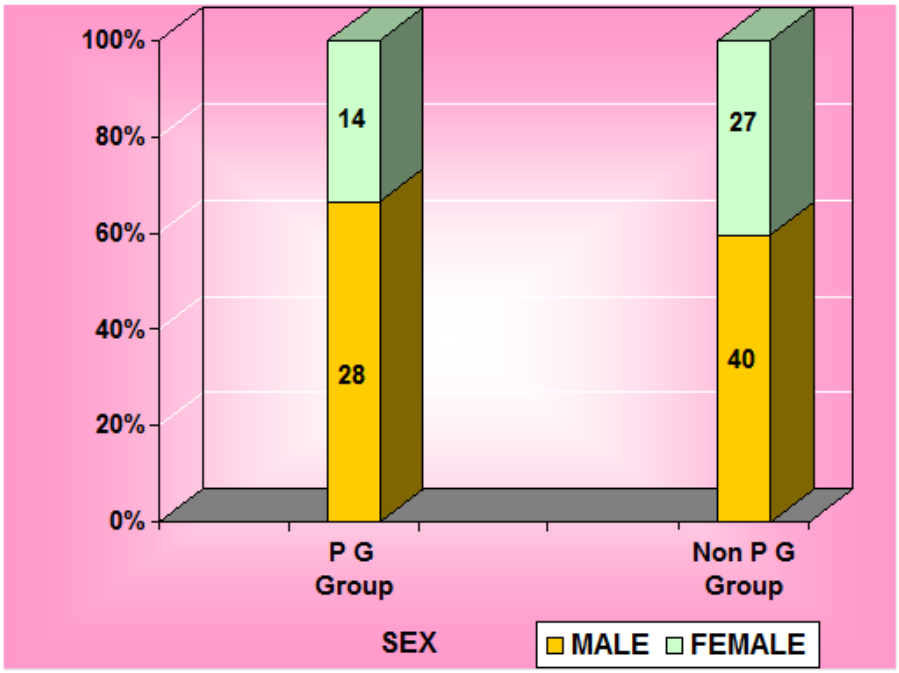
Sex distribution

Males formed the majority with 62.3%. Among those in the PG analogue group 66.7% were males while in the Non PG analogue group 59.7% were males. No statistically significant co-relation was found. (p=0.598).

Table 5.2

Sex	No of Cases in			
	PG Group		Non PG Group	
	No	%	No	%
Male	28	66.7	40	59.7
Female	14	33.3	27	40.3
'p'	0.598 Not Significant			

Figure 5.2



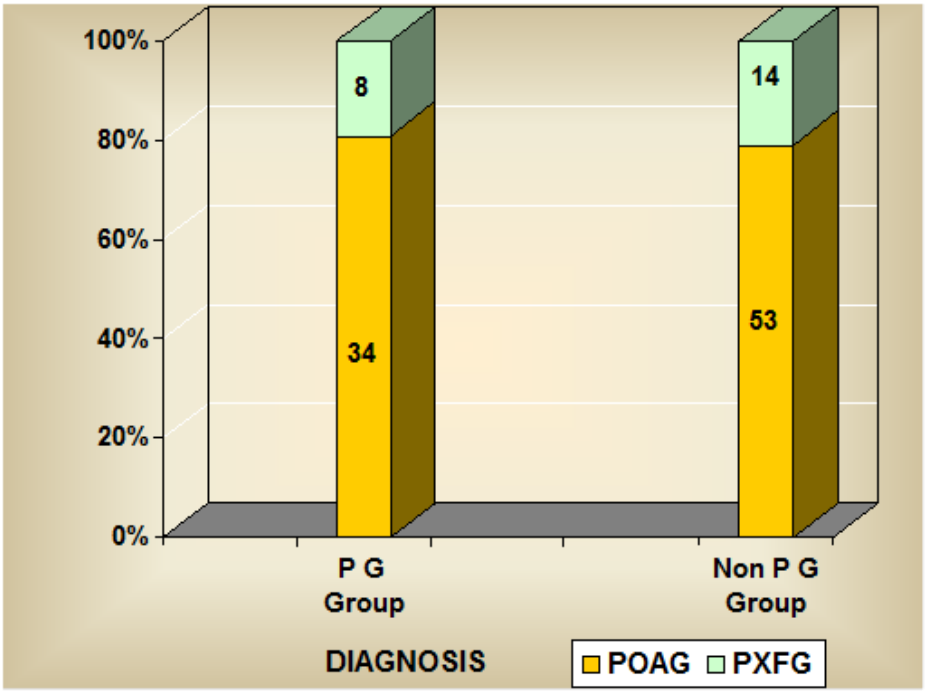
Diagnosis

Among the total number of cases 87 (79.8%) had Primary open angle glaucoma while 22 patients were diagnosed with Pseudoexfoliation glaucoma. Among the PG analogue group 81% had POAG while among the Non PG analogue group it was 79.1% with POAG.

Table 5.3

Diagnosis	No of Cases in			
	PG Group		Non PG Group	
	No	%	No	%
POAG	34	81.0	53	79.1
PXFG	8	19.0	14	20.9
'p'	0.991 Not Significant			

Figure 5.3



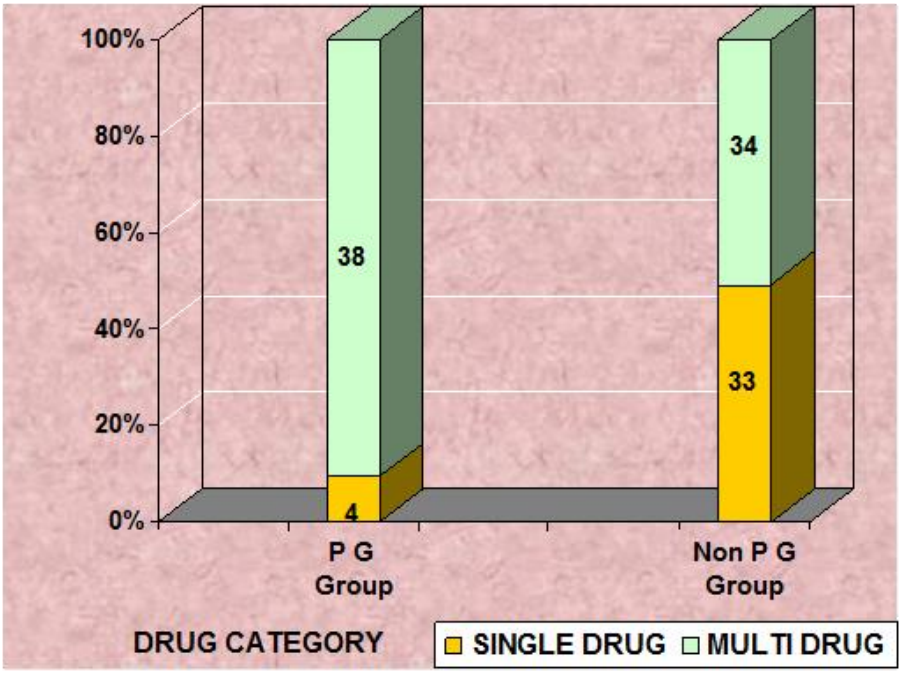
Drug Category

42 patients were in the PG analogue group while 67 were in the Non-PG analogue group. (Table 5.4) Among the PG analogue group 90.5% were on combination therapy while 50.7% were combination therapy in the Non-PG analogue group.

Table 5.4

Drug Category	PG Group		Non PG Group	
	No	%	No	%
Single drug PG Analogue	4	9.5	-	-
Single drug Non PG Analogue	-	-	33	49.3
Multidrug PG Analogue	38	90.5	-	-
Multidrug Non PG Analogue	-	-	34	50.7
Total	42	100.0	67	100.0

Figure 5.4



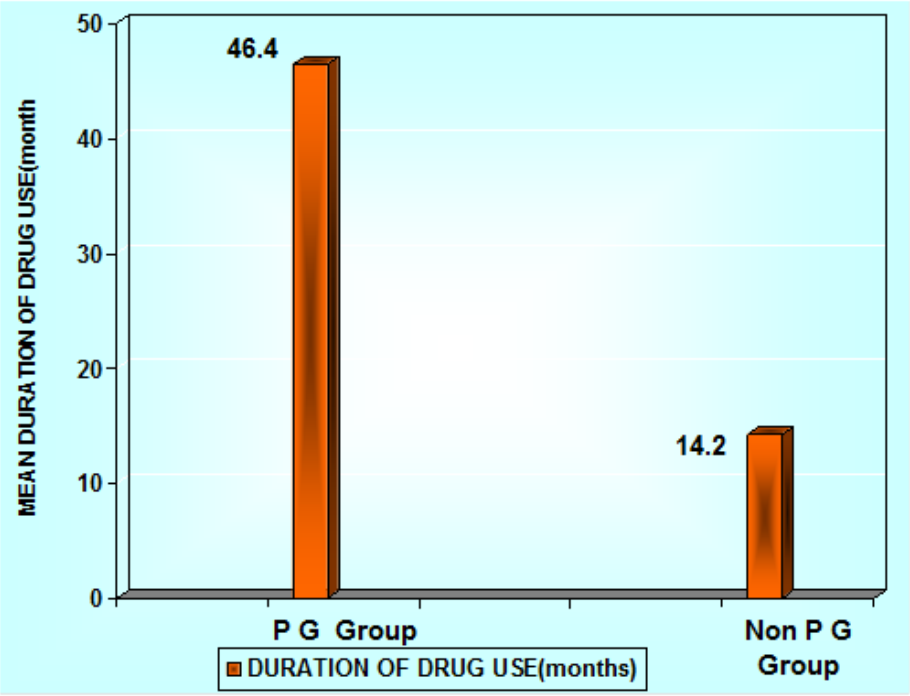
Duration of therapy till surgery

Mean duration of drug use was higher in the PG analogue group 46.4 months (SD 42.7months) compared to the Non PG analogue group 14.2 months (SD 14.1 months) which was statistically significant. ($p<0.001$).

Table 5.5

Duration of Drug Use	PG Group		Non PG Group	
	No	%	No	%
< 6 months	8	19.0	28	41.8
6 – 12 months	7	16.7	16	23.9
1 – 5 yrs	14	33.3	23	34.3
Above 5 yrs	13	31.0	-	-
Range	3 – 144 months		2 – 60 months	
Mean	46.4 months		14.2 months	
SD	42.7 months		14.1 months	
'p'	**<0.001 Significant**			

Figure 5.5



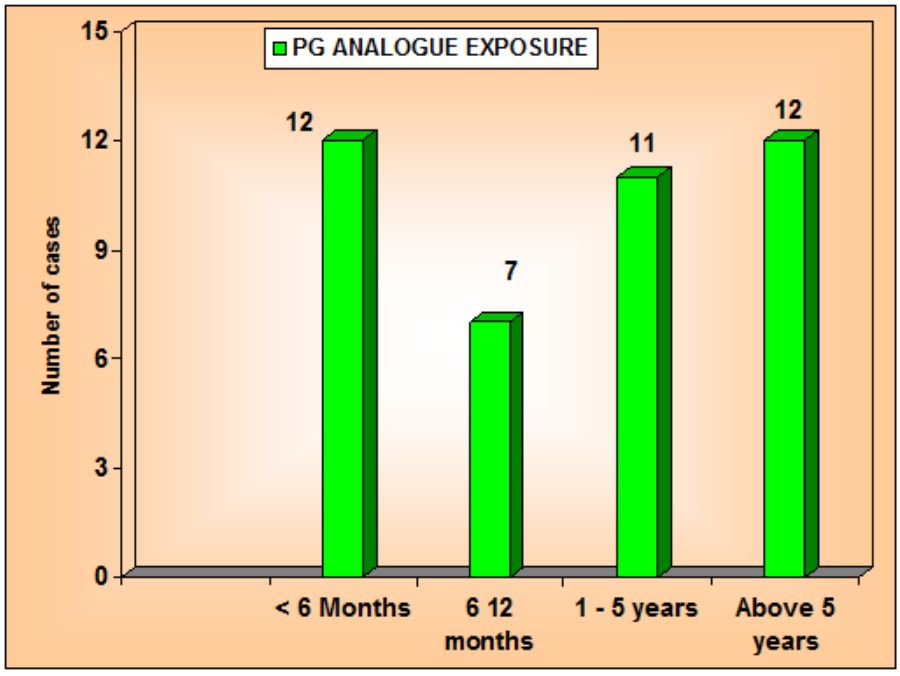
Exposure to PG analogue

Among those in the PG analogue group, the mean exposure to prostaglandin analogues was 40.4 months with a SD of 42.3 months.

Table 5.6

PG Analogue exposure	No of Cases in PG Group	
	No	%
< 6 months	12	28.6
6 – 12 months	7	16.7
1 – 5 yrs	11	26.2
Above 5 yrs	12	28.6
Total	42	100.0
Range	0 – 144 months	
Mean	40.4 months	
SD	42.3 months	

Figure 5.6



Intraocular Pressure

At pre-operative period, Mean (SD) IOP was 18.1(±7) mmHg in PG analogue group and 18.1(4.5) mmHg in Non-PG analogue group which was found to be statistically significant ($p < 0.001$) (Table 5.7). At end of 6 months, IOP decreased to 15.0(±5.2) mmHg in PG analogue group and 13.3(3.6) mmHg in Non-PG analogue group. Statistically significant difference betweent the groups was seen at 1 month (p=0.037) and 3 month (p=0.003) follow-ups postoperatively. Final IOP however was lower in Non-PG analogue group compared to PG-analogue group though without statistical significance (P=0.051) (Table 5.8)

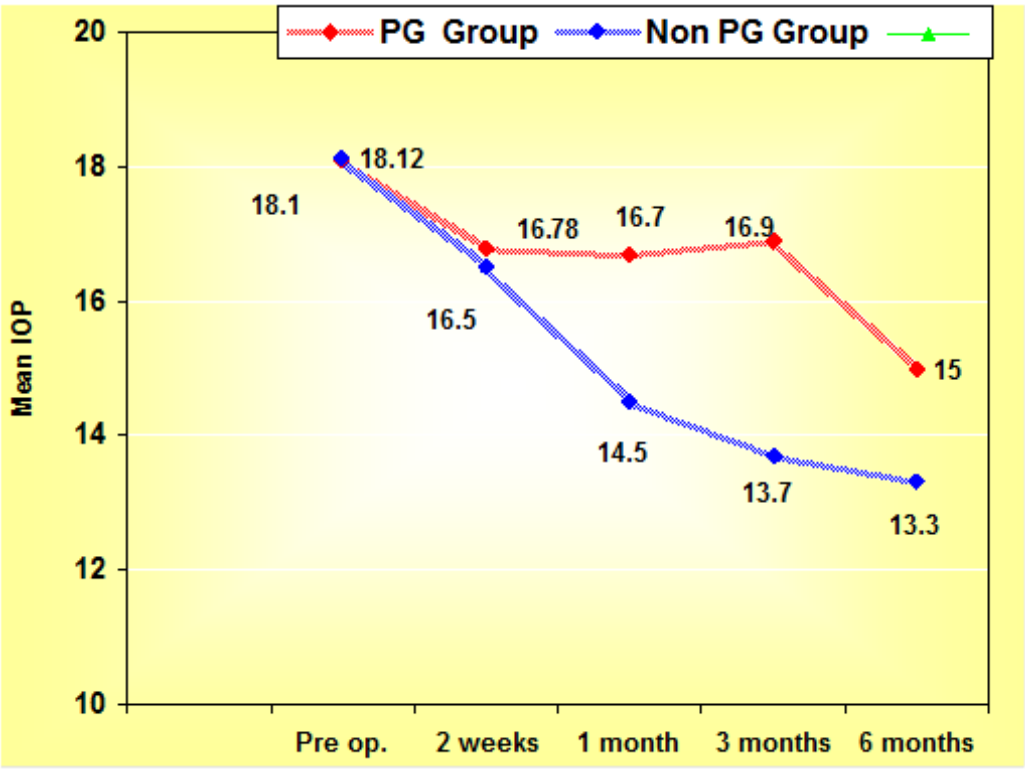
Table 5.7

Period	**I O P**	
	Mean	**S.D.**
Pre operative	18.11	5.57
Post Operative	13.88	4.3
'p'	**< 0.001 Significant**	

Table 5.8

Period	IOP (mm/Hg)				'p'	Significance
	PG Group		Non PG Group			
	Mean	SD	Mean	SD		
Pre operative.	18.1	7.0	18.1	4.5	0.983	Not Significant
2 weeks follow up	16.7	5.6	16.5	5.7	0.88	Not Significant
1 month follow up	16.7	6.2	14.5	4.6	**0.037**	**Significant**
3 months follow up	16.9	7.7	13.7	4.0	**0.007**	**Significant**
6 months follow up	15.0	5.2	13.3	3.6	0.051	Not Significant

Figure 5.7



Visual acuity

Table 5.9 shows the results of visual acuity recorded in the pre-operative visit and on post-operative follow up (2 weeks, 1 month, 3 months and 6 months) Mean visual acuity between PG group and non PG group showed no statistically significant difference in each visit ($p>0.05$). Statistically significant difference was seen between the preoperative and postoperative visual acuity as shown in Table 5.10.

Table 5.9

Period	BCVA – Log MAR				'p'	Significance
	PG Group		Non PG Group			
	Mean	SD	Mean	SD		
Pre-operative.	0.57	0.29	0.6	0.3	0.613	Not Significant
2 weeks follow up	0.112	0.149	0.149	0.188	0.342	Not Significant
1 month follow up	0.1	0.138	0.11	0.187	0.755	Not Significant
3 months follow up	0.086	0.127	0.11	0.193	0.501	Not Significant
6 months follow up	0.08	0.125	0.1	0.182	0.5	Not Significant

Figure 5.8

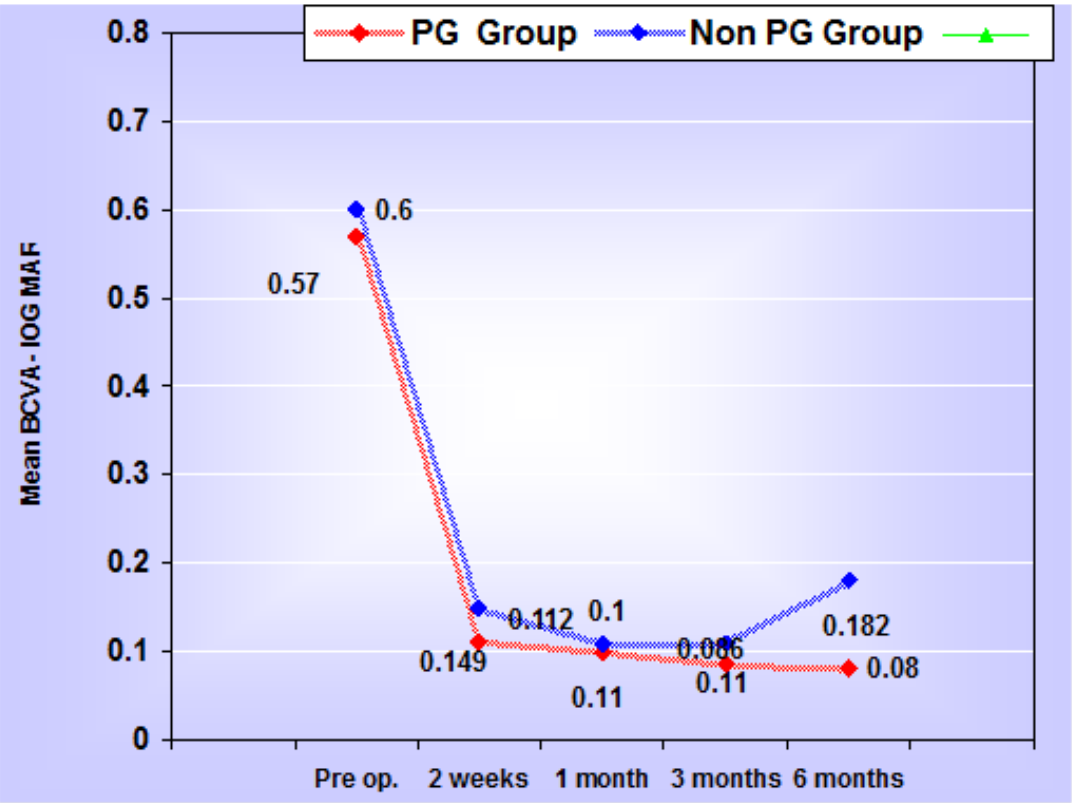


Table 5.10

Period	Visual acuity	
	Mean	**S.D.**
Pre-operative	0.71	1.42
Post-Operative	0.09	0.164
'p'	**< 0.001 Significant**	

Post-Operative Medications

Table 5.11 shows the number of postoperative antiglaucoma medications needed in both groups for control of Intraocular pressure. No statistically significant difference was found, however at 3 month and 6 months follow-up, patients on the PG analogue group required slightly higher number of medications.

Table 5.11

Number of medications at	Category				'p'
	P G		NON PG		
	Mean	S.D.	Mean	S.D.	
2 weeks	0.048	0.309	0.03	0.172	0.7 Not Significant
1 month	0.128	0.469	0.179	0.548	0.629 Not Significant
3 months	0.528	0.941	0.185	0.556	0.051 Not Significant
6 months	0.694	1.064	0.409	0.803	0.131 Not Significant

Final visit medication

At the final follow up of 102 cases , 23 cases (63.89%) in the PG analogue group did not require any additional glaucoma medications, in 5 cases (13.89%) one anti-glaucoma medication was added to control the IOP, 8 cases (22.2%) required 2 or more anti-glaucoma medications to control the IOP. In the non PG analogue group 50 cases (75.76%)did not require any additional glaucoma medications, in 7 cases (10.61%) one anti-glaucoma medication was required to control the IOP and the rest 9 cases (13.63%) required 2 or more anti-glaucoma agents for IOP control. No statistically significant co-relation was found, the number of postop medications needed postoperatively was higher for the PG analogue group.

Table 5.12

	Number of Antiglaucoma medications			
Category	0	1	2 or more	
PG analogue	23	5	8	36 (35.3%)
Non PG analogue	50	7	9	66 (64.7%)
Total	73(71.6%)	12(11.8%)	17(16.7%)	102

Complications

Intraoperative complications encountered included one case of PCR with vitreous disturbance during phacoemulsification and one case of cheese wiring of the scleral flap during suturing. Both cases were managed well and did not have any significant sequelae and therefore not included under failure. Bleb needling with 5-FU(5mg/0.1ml) was done in 9 cases with 5 cases being done at 3 months postop. 5 cases were in PG analogue group and 4 cases in non-PG analogue group. There were no cases of bleb related infections or endophthalmitis in the study population. One patient in the PG analogue group underwent resurgery with glaucoma drainage device implantation (AADI) for failed surgery.

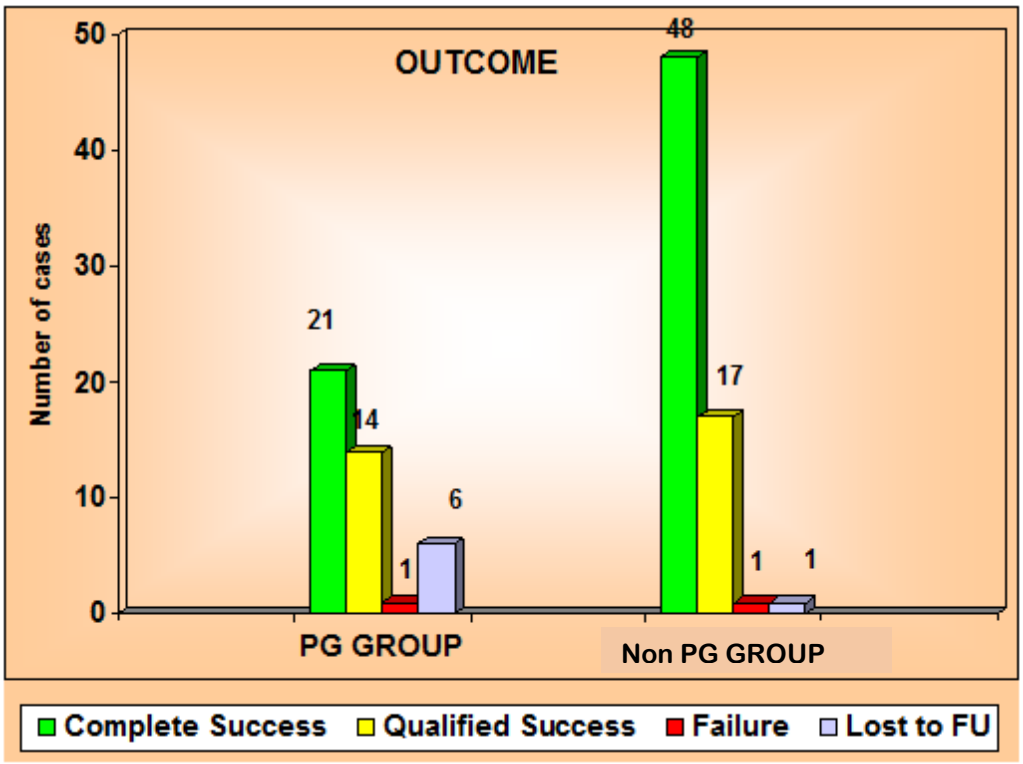
Surgical Outcome

Table 5.13 shows the surgical outcomes after 6 months among the PG and non PG analogue group. Though no statistically significant difference was found, the chances of successful filtration surgery were higher among the Non PG group compared to the PG analogue group.

Table 5.13

Outcome	Cases			
	PG Group		Non PG Group	
	No	%	No	%
Complete Success	21	50.0	48	71.6
Qualified Success	14	33.3	17	25.4
Failure	1	2.4	1	1.5
Complete Failure	-	-	-	-
Lost to follow up	6	14.3	1	1.5
'p'	0.206 Not Significant			

Figure 5.9



No statistically significant correlation was seen between diagnosis or total duration of preoperative medications with outcome as shown in Table 5.14 and Table 5.15.

Table 5.14

Diagnosis	**Outcome**			
	Success		**Failure**	
	No	**%**	**No**	**%**
POAG	53	65.4	28	24.6
PXFG	16	76.2	5	23.8
'p'	0.498 Not Significant			

Table 5.15

Outcome	**Total duration of drugs pre-operatively(months)**	
	Mean	**S.D.**
Complete Success	22.1	28.9
Qualified Success	36.4	36.0
Failure	5.5	3.5
Complete Failure	-	-
Lost to follow up	7.7	7.2
'P'	0.095 Not significant	

Histopathology – Conjunctival Analysis

Table 5.16 shows the results following histopathological analysis of 22 specimens Though there was no statistical significance, the numbers of goblet cells and plasma cells were more in the PG analogue group while the number of mast cells were more in the non PG analogue group suggestive of more subclinical inflammation and fibrosis potential in the non PG analogue group.

Table 5.16

	PG. Group		Non PG Group		
	Mean	**S.D.**	**Mean**	**S.D.**	**'p'**
G.C.	1.63	2.41	0.28	0.4	0.069 Not significant
IELC	2.22	1.43	3.37	2.81	0.288 Not significant
SELC	8.75	6.5	8.28	5.8	0.859 Not significant
Mast Cells	1.72	1.31	1.92	1.46	0.742 Not significant
Plasma Cells	1.27	2.99	0.03	0.1	0.165 Not significant

Figure 5.10

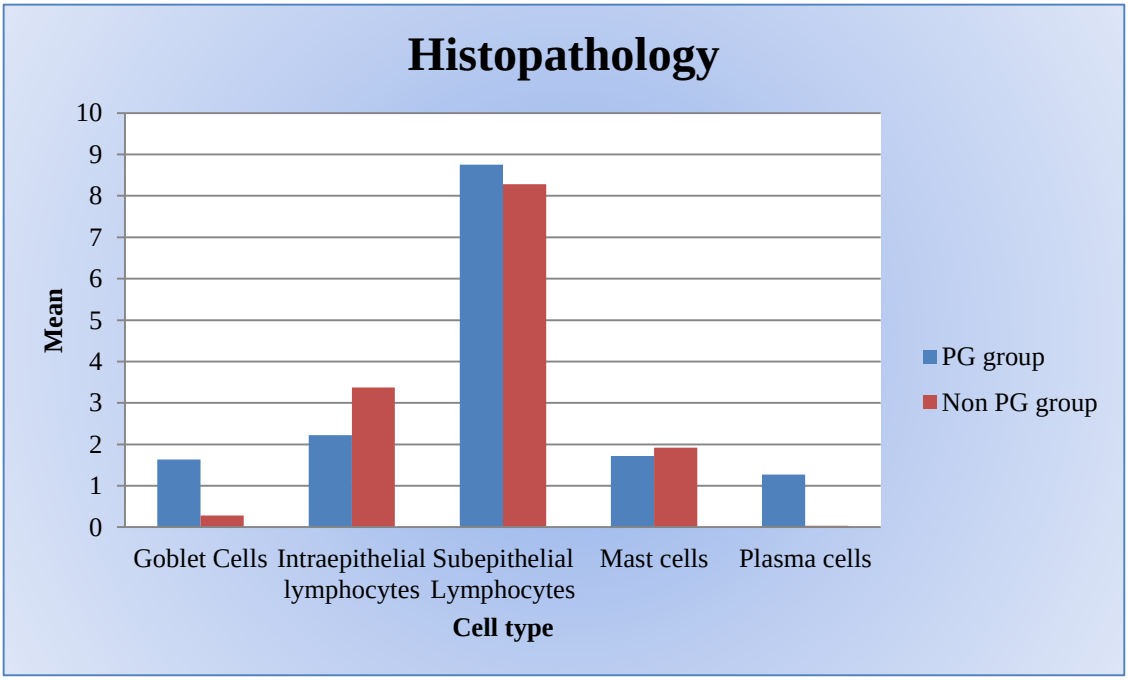


Figure 5.11. Stroma with increased mast cells and fibrosis

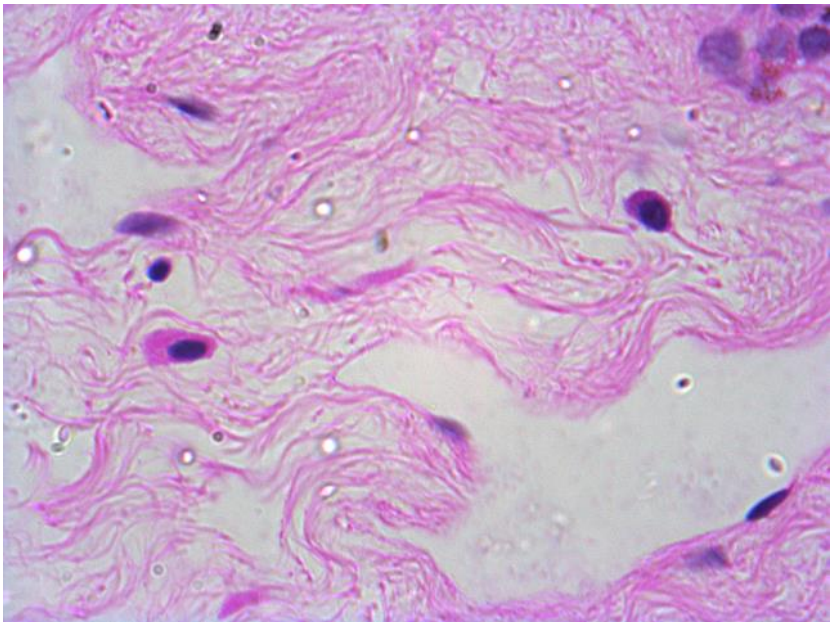


Figure 5.12. Inflammatory epithelium and stroma with increased epithelial and subepithelial lymphocytes

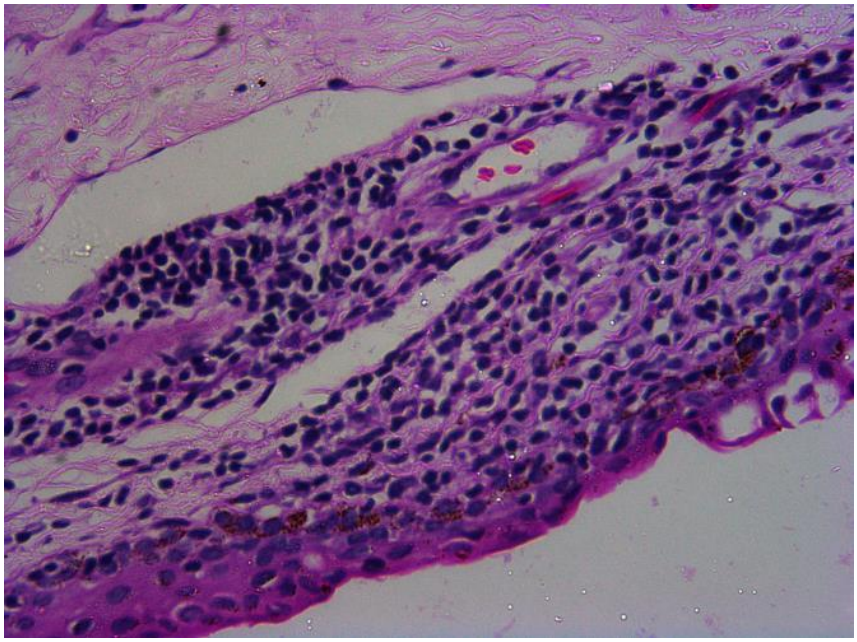


Figure 5.13. Epidermadised epithelium with reduced goblet cells

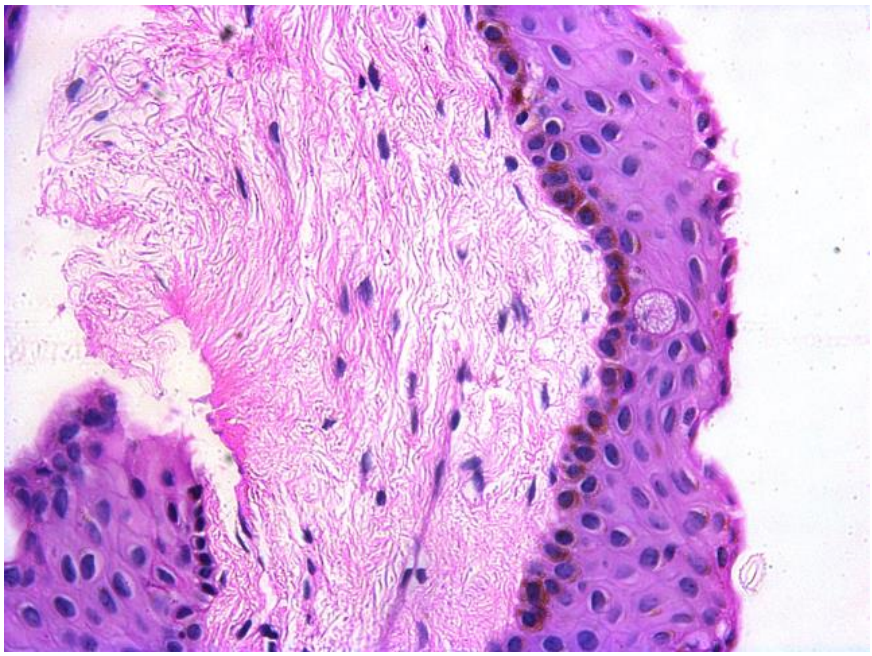
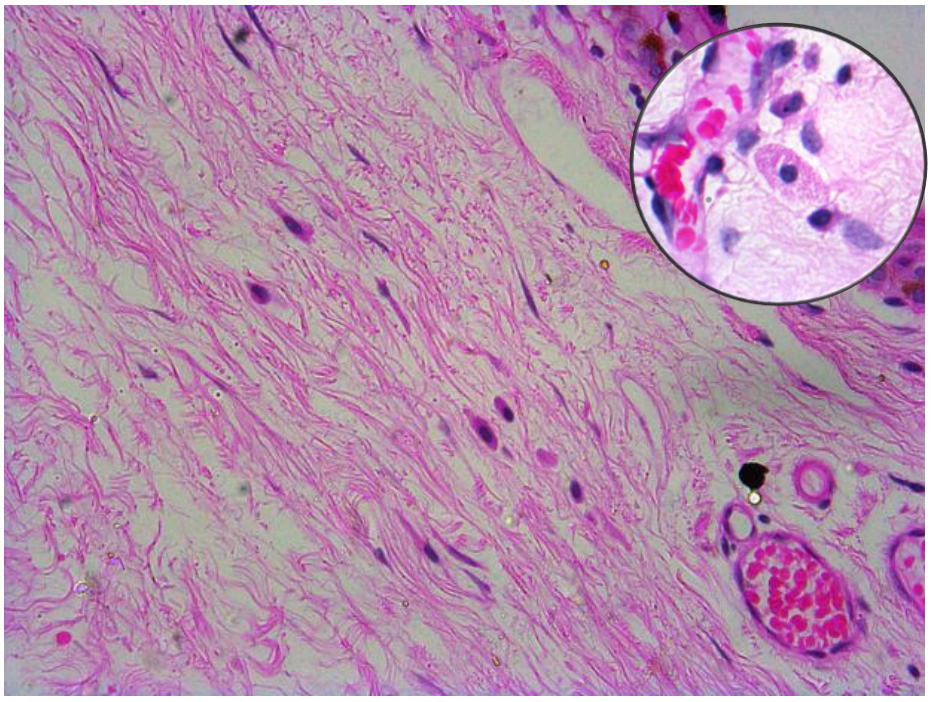


Figure 5.14. Fibrotic stroma with increased mast cells

Inlet showing degranulating mast cell



Conjunctival analysis and Surgical outcomes

Table 5.17 shows the surgical outcomes among the patients who underwent conjunctival biopsies. Though no statistically significant correlation was found between the cell count and surgical outcome, sub-epithelial lymphocytes, mast cells and plasma cells were shown to be lesser among patients with successful surgical outcomes after 6 months.

Table 5.17

	Outcome						
	Success		**Qualified success and Failure**		**Lost to follow up**		**'p'**
	Mean	**S.D.**	**Mean**	**S.D.**	**Mean**	**S.D.**	
G.C.	1.06	2.27	0.81	1.02	0.44	0.19	0.865 Not significant
IELC	2.52	1.76	3.71	2.94	1.67	1.86	0.391 Not significant
SELC	6.57	4.12	12.9	7.69	5.89	2.14	0.052 Not significant
Mast Cells	1.76	1.14	2.05	1.93	1.56	1.02	0.862 Not significant
Plasma Cells	0.08	0.29	1.57	3.59	0.33	0.58	0.321 Not significant

DISCUSSION

The main goal of glaucoma filtration surgery is to achieve a good functioning bleb with less complications and adequate reduction in intraocular pressure. An ideal bleb should be diffuse, with minimal elevation, relatively avascular with conjunctival microcysts. Many factors play a role in achieving this outcome. The most important being, the wound healing process in the conjunctival tissue which is greatly influenced by the degree of subconjunctival inflammation and fibrosis as shown in most previous studies. One of the main factors linked with an increase in failure rates is use of preoperative medications.

In our study of 109 eyes of 109 patients, 87 were POAG while the rest had pseudoexfoliation glaucoma. Forty two patients had received PG analogues prior to surgery while the rest 67 patients were on other antiglaucoma agents such as beta-blockers, carbonic anhydrase inhibitors and α- adrenergic agonists.

The pre-operative characteristics were comparable in both the groups with respect to the age, sex, pre op IOP and visual acuity.

With respect to the duration of therapy prior to surgery, PG analogue group had a significantly higher mean duration of use compared to the non PG analogue group.

Post-operative mean visual acuity between PG and Non PG analogue group showed no statistically significant difference in each visit ($P>0.05$). In each group, pre-operative and Final follow-up showed statistically significant improvement in visual acuity ($P<0.001$).

The post-operative IOP reduction was significant at the end point in both the groups. The IOP reduction in the PG and Non PG group did not show any statistically significant difference in the initial and final follow-ups. These however did show a statistically significant difference at the 1 month and 3 month visits with PG analogue group recording higher IOP reading as compared to the non PG analogue group ($p<0.05$)

Intraoperative complications were seen in only 2 cases with one case of Posterior capsular rent occurring during phacoemulsification and another case of cheese wiring of the scleral flap while suturing. While the former had successful surgical outcome, the latter required bleb needling postoperatively for bleb fibrosis.

50% of the PG analogue group and 71.6% of the Non PG analogue group had complete success while 33.33% of the PG group and 25.4% of the Non PG analogue group had qualified success. Failure was seen in only 2 cases with one needing resurgery with glaucoma drainage device for IOP control while another had unexplained reduced visual acuity postoperatively despite IOP control. Although there was no statistically

significant difference between the 2 groups the chance of surgical success was slightly higher in the non PG analogue group.

Previously conducted clinical and experimental studies have provided strong evidence that chronic use of antiglaucoma medications can induce ocular surface changes resulting in discomfort, inflammation, tear film instability and subconjuctival fibrosis which have been shown to be directly proportional to the duration of treatment and the type of medication used.(103,124,130–132)

Sherwood et was one of the first to prove this by comparing the conjunctiva of patients who underwent primary surgery compared to those who were treated with topical medications prior to surgery and was able to show beyond doubt that medical therapy prior to surgery increases the number of tissue inflammatory cells and thus enhance the risk of external bleb scarring post filtration surgery. He showed a significant increase in the number of macrophages, lymphocytes, fibroblasts, and mast cells in both the substantia propria of the conjunctiva and the Tenon's capsule of patients who had received long-term topical antiglaucoma medication. The drawback however was the low number of samples and that the type of medication used was not taken into consideration. Also currently used drugs like beta-blockers or

prostaglandin analogues were not available back then and hence this study.(22)

Similar reports were also given by Lavin et al and Longstaff et al which noted long term use of topical antiglaucoma medications as a significant risk factor for surgical failure.(21,23)

Our study most closely resembles the series of published literature by Broadway et al who studied the antiglaucoma agent induced conjunctival changes, outcomes of surgery and effects of reversal of those conjunctival changes by topical steroids.(56) However as prostaglandin analogues have made their entry to the arsenal only recently, little information is available about their influence. Russ et al compared the effects of prostaglandin analogues and timolol maleate in the rabbit conjunctiva and demonstrated that timolol induced more severe changes as compared to prostaglandin analogues which could be the consequence of enhanced fibroblast activity. They also reported increased goblet cell count in patients treated with prostaglandin analogues, a change not seen with timolol.(115,133) Terai et al who compared the effect of timolol and latanoprost on the human conjunctiva found the latanoprost treated group to have lesser inflammatory reaction than the timolol group. The study also found an up regulation of CD68 antibodies, an indicator for acute and chronic inflammation, among the timolol group and concluded that

latanoprost therapy might have a more favourable effect on the outcome of trabeculectomy. (116) Similarly in our study we found an increase in goblet cells among the PG analogue group and increase in mast cells in the non PG analogue group though there was no statistical significance. This is in accordance to other studies by Sherwood et al, Baudouin et al and Herreras et which demonstrated that timolol may induce a drop in goblet cells and crystallization pattern associated with keratoconjunctivitis sicca.(124,134)

Similar conclusions were also made by Pisella et al who compared in vitro and in vivo effects and showed while unpreserved formulations were definitely better, preserved latanoprost caused less toxicity than preserved timolol and may acutally have a protective effect against the toxicity caused by BAK.(117)

Thus in our study while there was no statistically significant difference in surgical outcomes between the 2 groups, the postoperative intraocular pressures were found to be higher in the PG analogue group. Interestingly the conjunctival biopsies did show higher goblet cell counts in the PG group, the subclinical inflammation was found to be higher among the Non PG analogue group even though the mean duration of treatment was found to be significantly higher in the PG analogue group.

Limitations and Recommendations

The limitations of our study were

1. Short follow-up period
2. Involvement of multiple surgeons.
3. Inclusion of both POAG and Pseudoexfoliation glaucoma which could influence the outcome of surgery
4. No specific preoperative drug protocol.
5. Effects of preservative used was not taken into consideration
6. Not a randomised control trial
7. Significant difference in the duration of medical treatment between the 2 groups
8. Insufficient or inadequate biopsy specimens

Recommendations

A single surgeon, randomised control trial with preservative free medications, longer follow-up period and standard preoperative regimen comparing the different PG analogues will be able to throw further light into the outcomes of surgery in these patients.

CONCLUSION

To conclude, in our study, we have found that while different drugs and the duration of use do influence the outcome of filtration surgery, there is no statistically significant difference in outcomes after preoperative use of prostaglandin analogues as compared with other agents. In accordance with previous studies, histopathologically, the conjunctival changes induced by prostaglandin analogues were more favourable to better surgical outcomes as compared with aqueous suppressants. The postoperative intraocular pressure reduction postoperatively however was found to be lesser and statistically significant at 1 and 3 month follow-ups for the Non PG analogue group compared to PG analogue group. A randomised controlled trial with longer follow-up and lesser confounding factors is necessary to put this debate to rest.

ANNEXURE

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ABBREVIATIONS

POAG	-	PRIMARY OPEN ANGLE GLAUCOMA
PACG	-	PRIMARY ANGLE CLOSURE GLAUCOMA
PXFG	-	PSEUDOEXFOLIATION GLAUCOMA
IOP	-	INTRA OCULAR PRESSURE
MMC	-	MITOMYCIN C
5-FU	-	5-FLUOROURACIL
AC	-	ANTERIOR CHAMBER
OHT	-	OCULAR HYPERTENSION
BCVA	-	BEST CORRECTED VISUAL ACUITY
SD	-	STANDARD DEVIATION
MD	-	MEAN DEVIATION
PCR	-	POSTERIOR CAPSULAR RUPTURE
IOL	-	INTRAOCULAR LENS
BSS	-	BALANCE SALT SOLUTION
PG ANALOGUE - PROSTAGLANDIN ANALOGUE		
LSL	-	LASER SUTURE LYSIS
RSR	-	RELEASABLE SUTURE REMOVAL
AADI	-	AUROLAB AQUEOUS DRAINAGE DEVICE
GDD	-	GLAUCOMA DRAINAGE DEVICE
GC	-	GOBLET CELL
IELC	-	INTRA - EPITHELIAL LYMPHOCYTES
SELC	-	SUB-EPITHELIAL LYMPHOCYTES
MC	-	MAST CELL
PC	-	PLASMA CELL

CONSENT FORM

Informed Consent form to participate in a clinical trial

Study Title: **Outcome of glaucoma surgery in patients on prostaglandin analogues**

Protocol Number:

Subject's Name: _____Subject's Initials: _____

- Subject ID No: _____
- Date of Birth / Age: _____

		Please put initial
1.	I confirm that I have understood the information about the study, procedures and treatments for the above study and have had the opportunity to ask questions and I have received satisfactory answers to all of my questions. I have been given a copy of the informed consent form to take home.	[ ]
2.	I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. However this may not be possible for certain surgical procedures.	[ ]

3.	I understand that the Investigator of the study wants to access my health records for research purpose. However I understand that my identity will not be revealed or information released to third parties or published.	[ ]
4.	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	[ ]
5.	I agree to take part in the above study	[ ]

Signature (or Thumb impression) of the Subject:

_____

Date: _____/_____/_____

Subject's Name:

_____

Signature (or Thumb impression) of Legally Acceptable Representative (LAR):

_____ Date:

_____

Signature of the Investigator: _____Date:

_____/_____/_____

Investigator's Name:

_____

Signature of the Witness _____

Date: _____/_____/_____

Name of the Witness:

_____

PROFORMA

Outcome of glaucoma surgery in patients on prostaglandin analogues

Study sample Number | | | | |

EYE – RIGHT / LEFT

Date dd/mm/yy

Patient details

Name

MR No

Age_____ years

Gender (M /F)

History

Age at diagnosis _____years

Time since diagnosis _____years _____months

IOP at first presentation _____mm Hg

Treatment History (current)

Sl No.	Drug	Conc.	Dose (drop/ day)	Exposure (yrs)	Preservative (with conc.)	Brand

Treatment history (prior)

Sl No.	Drug	Conc.	Dose (drop /day)	Exposure (yrs)	Preservative (with conc.)	Brand

Systemic history (Please tick the appropriate ones)

DM / HTN / Cardiac / Stroke / Others (please mention below)

Pre-op Ocular Examination

	Right	Left
BCVA Distance		
BCVA Near		

Anterior Segment

Lids		
Conjunctiva		
Cornea		
AC		
Iris		
Pupil		
Lens		
IOP		

Anterior segment findings suggesting drug intolerance (mention if any)

Was topical therapy stopped prior to surgery (YES/NO) If yes mention drug and duration since stopped.

Fundus

Media			
Disc	Size Colour Margin CDR NRR		
Blood vessels			
Macula			
Others			

CCT		
Axial length		

Diagnosis

Surgery Details

Type	
Date	
Block used	
Bridle suture (Sup Rectus/ Corneal traction)	
MMC use (if present/not)	
Postop Medications advised	

Intraop Complication Report

Traction suture related	
Conjunctival Flap related	
MMC application	
Scleral flap related	
Corneal injury	
Iridectomy related	
Others (Mention if any)	

Histopathological Report

Cell type	Number
Goblet cells	
Intraepithelial Lymphocytes	
Intrastromal lymphocytes	
Mast cells	
Plasma cells	

Follow Up

DD / MM / YY

1st Post-op visit Date | | | | | | |

BCVA		
Applanation tonometry		
Bleb description		
Fundus		
Complications		
Needling/Suture lysis/Suture release		

Antiglaucoma medications

2nd Post-op visit Date | | | | | | |

BCVA		
Applanation tonometry		
Bleb description		
Fundus		
Complications		
Needling/Suture lysis/Suture release		

Antiglaucoma medications

3rd Post-op Visit Date | | | | | | |

BCVA		
Applanation tonometry		
Bleb description		
Fundus		
Complications		
Needling/Suture lysis/Suture release		

Antiglaucoma medications

ARAVIND MEDICAL RESEARCH FOUNDATION
Institutional Ethics Committee
(REGISTRATION NO. ECR/182/INST/TN/2013 DATED 20.04.2013)

12th December 2015

To
Dr. Aswin PR
MS Resident
Aravind Eye Hospital
Madurai

Dear Dr. Aswin,

Thesis Title: Outcome of glaucoma surgery in patients on prostaglandin analogues

IRB Code: IRB201600222

Thank you for submitting your thesis and seeking the approval from the ethics committee. The documents provided by you for consideration which include the thesis protocol and informed consent forms were reviewed for the research methodology and scientific content. The Ethical committee did not find any correction and has recommended the thesis to go ahead in the present form.

Thanking you

Yours Sincerely,

S. Lalitha

Dr.Lalitha Prajna
Member Secretary
Institutional Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
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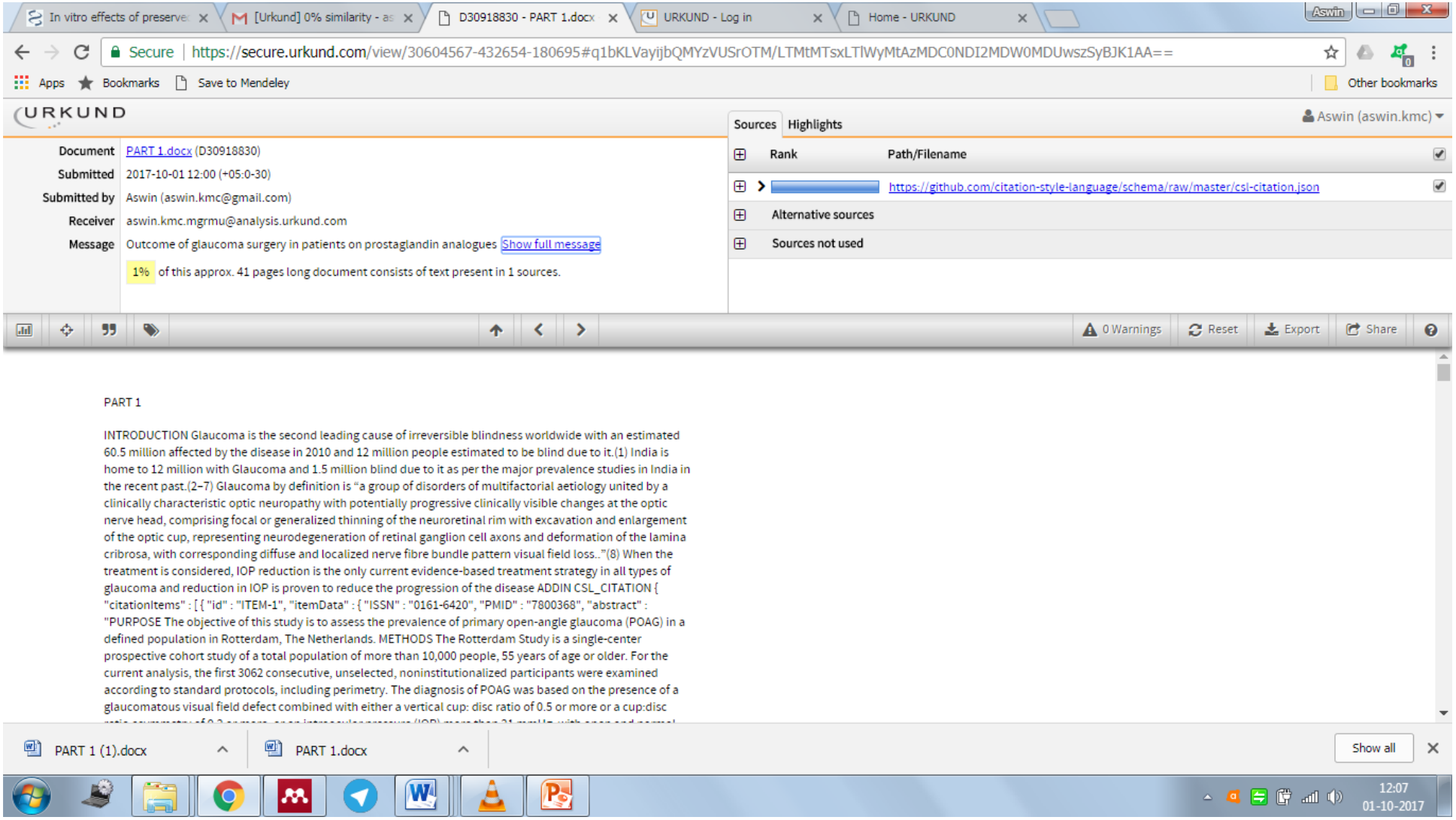
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PART 1
INTRODUCTION Glaucoma is the second leading cause of irreversible blindness worldwide with an estimated 60.5 million affected by the disease in 2010 and 12 million people estimated to be blind due to it.(1) India is home to 12 million with Glaucoma and 1.5 million blind due to it as per the major prevalence studies in India in the recent past.(2–7) Glaucoma by definition is "a group of disorders of multifactorial aetiology united by a clinically characteristic optic neuropathy with potentially progressive clinically visible changes at the optic nerve head, comprising focal or generalized thinning of the neuroretinal rim with excavation and enlargement of the optic cup, representing neurodegeneration of retinal ganglion cell axons and deformation of the lamina cribrosa, with corresponding diffuse and localized nerve fibre bundle pattern visual field loss.."(8) When the treatment is considered, IOP reduction is the only current evidence-based treatment strategy in all types of glaucoma and reduction in IOP is proven to reduce the progression of the disease ADDIN CSL_CITATION { "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "ISSN" : "0161-6420", "PMID" : "7800368", "abstract" : "PURPOSE The objective of this study is to assess the prevalence of primary open-angle glaucoma (POAG) in a defined population in Rotterdam, The Netherlands. METHODS The Rotterdam Study is a single-center prospective cohort study of a total population of more than 10,000 people, 55 years of age or older. For the current analysis, the first 3062 consecutive, unselected, noninstitutionalized participants were examined according to standard protocols, including perimetry. The diagnosis of POAG was based on the presence of a glaucomatous visual field defect combined with either a vertical cup: disc ratio of 0.5 or more or a cup:disc
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URKUND

Urkund Analysis Result

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Sources included in the report:

https://github.com/citation-style-language/schema/raw/master/csl-citation.json

Instances where selected sources appear:

2

Study no	MR No.	EYE	Age	Gender	Diagnosis	Medication started on	Drugs used and Duration	PG 1 NONPG 2	Category	Total Duration	PG analogue exposure	Pre-op IOP	Pre-op BCVA	Axial Length	Date of surgery	Complications	Follow Up 2 WEEKS						Follow Up 1 month						Follow Up 3 months						Last follow-up 6 months						Outcome	CCT
													LogMAR				POD	BCVA	IOP	Bleb description	AGM	Secondary procedure	Date	BCVA	IOP	Bleb description	AGM	Secondary procedure	Date	BCVA (logMAR)	(mmHg)	Bleb description	AGM	y Procedur	Date	(logMAR)	IOP (mmHg)	Bleb description	AGM	Secondary Procedure		
1	3933991	2	77	1	1	Dec-14	Misopt BDIobrim BD	2	4	24	0	15	0.3	21.63	06-02-2016	0	23-02-16	0.20	17	low bleb	none	released	29-03-16	0.00	14	bleb+	none	Apical LSL	23-03-16	0.48	17	low bleb	none		26-04-16	0	12		none	0	1	0.502
2	4103773	2	81	2	1	04-03-2011	Alphagan Z+ Latacom 15/8/15	1	3	60	6	13	0.3	21.79	13-02-2016	0	01-03-16	0.00	11	bleb+	0	LSL	12-03-16	0.00	19	bleb+	0	LSL	28-03-16	0.20	12	bleb+	0	RSR	13-08-16	0.20	12	low bleb	0	0	1	0.545
3	4136026	1	76	1	2	Aug-15	Britiblu BD	2	2	21	0	22	0.5	22.41	13-02-2016	0	01-03-16	0.60	21	flat bleb	none	removed +	18-03-16	0.50	18	low bleb		removed	01-04-16	0.50	15	low bleb		apical LSL	08-07-16	0.5	13	low bleb	0	0	1	0.519
4	4209495	1	65	1	2	01-10-2015	Timoler BD	2	2	3	0	18	1.5	23.1	13-02-2016	iris incarcerated sideport	19-02-16	0.20	26	vascularised bleb	Timolet BD	apical LSL	01-03-16	0.20	26	flat bleb	betabrim e/d BD	bleb needling+ iris repositioning	12-04-16	0.20	22	low bleb	Betabrim BD	none	12-08-16	0.20	16	low bleb	Betabrim BD	0	2	0.541
5	4167765	2	45	2	1	25-11-2015	Misopt e/d	2	2	3	0	28	0	22.72	13-02-2016	0	16-02-16	0.20	14	with	0	0	22-02-16	0.20	14	diffuse	0	0	26-02-16	0.20	11	bleb+	0	0	01-07-16	0.2	7	vascular bleb	0	0	1	0.584
6	4041103	2	60	1	2	20-05-2015	Combigan BDMonosopt BD	2	4	8	0	28	0.6	22.95	20-02-2016	0	05-03-16	0.00	16	low bleb	0	2 RS removed	21-03-16	0.00	14	vascualr bleb	0	apical LSL	09-04-16	0.00	10	bleb +	0	none	04-11-16	0	16	bleb+	0	0	1	0.568
7	3995517	1	60	2	2	13-03-2015	Betabrim e/d	2	2	10	0	20	0.5	23.24	20-02-2016	0	04-03-16	0.50	19	flat bleb	0	LSL	04-03-16	0.50	20		0	LSL	24-03-16	0.00	16	flat bleb	0	apical LSL	16-07-16	0	18	low bleb	0	0	1	0.535
8	4114907	1	69	1	2	01-09-2015	Bidin LS1-9-15Monosopt Auroprost 8/9/15	1	3	5	5	30	0.5	24.19	23-02-2016	0	09-03-16	0.20	22	bleb+		nasal LSL	23-03-16	0.20	16	low bleb		LSL temporal	23-05-16	0.20	13	bleb+	0	0	20-06-16	0.20	12	bleb+	0	0	1	0.535
9	3648757	2	58	1	1	28-08-2013	Iotim e/d	2	2	24	0	14	1.07	22.4	25-02-2016	0	25-02-16	0.00	15	low bleb	0	LSL	05-04-16	0.00	16	low bleb	0	LSL	03-05-16	0.20	12	low bleb	0	LSL	31-08-16	0.17	10	low bleb	0	0	1	0.535
10	3659017	2	60	1	1	17-10-2013	Brimolol BD	2	4	24	0	16	0.77	23.52	26-02-2016	0	13-03-16	0.00	16	low bleb	0	LSL	26-03-16	0.00	13	vascularity	0	LSL	27-04-16	0.00	19		0	none	27-07-16	0	13	low bleb	0	0	1	0.519
11	4230215	2	72	1	1	01-01-2015	Timolol BD	2	2	12	0	18	0.3	23.24	01-03-2016	0	16-03-16	0.00	18	bleb+	0	RS removed	30-03-16	0.20	10	bleb	0	0	11-05-16	0.20	11	bleb+	0	0	15-07-16	0.2	11	low bleb	0	0	1	0.535
12	4080934	1	65	2	1	13-07-2015	Aurobrim Dorzox 13/7/15	2	4	8	0	12	0.3	22.76	01-03-2016	0	12-03-16	0.20	11	bleb+	0	RS removed	21-03-16	0.00	8	iris at ostium	0		04-04-16	0.50	10	bleb+	0	0	31-01-17	0.3	8	good bleb	0	0	1	0.519
13	4046645	2	63	2	1	24-06-2013	Betabrim Dorzox Bimat	1	3	72	36	19	0.8	22.47	02-03-2016	0	07-03-16	0.30	13	bleb+	0	LSL	28-03-16	0.30	13	bleb+	0	LSL	25-03-16	0.30	20	bleb+	Cibrim T	Bleb needling	11-10-16	0.3	18	fibrosed bleb	Cibrim T Dortas e/d	0	2	0.568
14	3297523	2	69	1	1	01-01-2011	Brimolol Dorzox	2	4	60	0	26	0.3	23.24	03-03-2016	PCR vitreous disturbance	07-03-16	0.20	18	flat vascularised bleb	0	LSL	21-03-16	0.20	15	low vascularised bleb	0	LSL	29-04-16	0.20	16	low bleb	0	LSL	22-08-16	0.20	16	low bleb	0	0	1	0.502
15	4121881	2	52	2	1	11-09-2015	Betabrim Auroprost	1	3	6	6	24	0.8	22.98	04-03-2016	0	18-03-16	0.00	22	bleb+	0	RSR	04-04-16	0.00	38	bleb	m	needling	11-04-16	0.00	18	bleb+	m	0	22-12-16	0	12	bleb+	Betabrim	0	2	0.535
16	3354662	2	79	1	1	09-12-2009	Travocom Alphagan Z	1	3	84	84	15	0.2	23.38	05-03-2016	0	11-03-16	0.20	20	vascularised bleb	Combigan	0	14-03-16	0.50	23	low bleb	Combigan	RSR	03-05-16	0.50	36	flat vascularised bleb	an D Lumigan	0	12-07-16	0.5	22	0	Combigan Lumigan Misopt	0	2	0.56
17	3059185	1	81	1	1	05-10-2010	Latanoprost Timolet	1	3	72	72	20	0.5	23.32	10-03-2016	0	28-03-16	0.20	12	low bleb	0	0	07-04-16	0.20	12	low bleb	0	0	16-04-16	0.20	14	bleb+	0	LSL	01-08-16	0.2	13	low bleb	0	RSR	1	0.567
18	4238872	1	48	2	1	2011	Iotim e/d	2	2	60	0	20	1	23.9	28-04-2016		18-05-16	0.00	18	low bleb	0	LSL	25-05-16	0.00	20	bleb on pressure	0	0	01-06-16	0.00	12	low bleb	0	0	08-12-16	0	13	fibrosed bleb	Combigan BD	0	2	0.535
19	3850808	2	70	1	1	23-07-2014	Misopt e/d Bidin	2	4	24	0	20	1	23.02	11-03-2016	iris pluggin to section, FM +	24-03-16	0.80	13	vascularised bleb	0	0	31-03-16	0.80	20	low bleb	0	LSL	16-04-16	0.80	14	bleb+	0	LSL	28-12-16	0.8	17	bleb+	Misopt E/D bd	0	2	0.535
20	3761771	2	64	1	1	11-03-2014	Betabrim Lupitros Monosopt	1	3	24	0	20	0.3	24.91	11-03-2016	0	05-04-16	0.20	21	fibrosing bleb	0	LSL	03-05-16	0.20	12	low diffuse bleb	0	LSL	07-05-16	0.20	18	bleb+	0	LSL	27-10-16	0.2	16	bleb+	Auroprost	0	2	0.502
21	4366420	2	68	1	1	03-10-2016	Auroprost and Alphagan Z	1	3	3	3	14	1	24.41	17-01-2017	0	01-02-17	0.00	12	low bleb	0	LSL	16-02-17	0.00	12	low bleb	0	LSL	06-03-17	0	12	good bleb	0	0	16-05-17	0	12	good bleb	0	0	1	0.551
22	4239319	1	70	1	1	12-01-2016	Combigan e/d	2	4	2	0	12	0.3	22.88	18-03-2016	0	02-04-16	0.00	14	bleb+	0	RS removed	16-04-16	0.00	16	good bleb	0	0	28-04-16	0.00	13	bleb+	0	0	09-09-16	0	8	good bleb	0	0	1	0.527
23	2332186	1	62	1	1	27-12-2006	Latanoprost+ Dorzox 11/12/15	1	3	120	120	10	0.2	22.98	19-03-2016	0	04-04-16	0.00	17	low bleb	0	RS removed	16-04-16	0.00	26	low bleb	Dorzox BD	apical LSL	30-04-16	0.00	8	low bleb	Dorzox BD	0	13-09-16	0	10	0	Dorzox BD	0	2	0.519
24	3562974	1	66	1	1	06-06-2013	brimodin Latoprost 8/9/14	1	3	36	24	15	0.2	22.31	20-01-2016	0	05-02-16	0.20	26	low bleb	0	LSL	19-02-16	0.20	20	low bleb	0	LSL	25-02-16	0.20	19	early fibrosis	0	LSL	17-11-16	0.2	15	low to flat bleb	0	NEEDLING 19/3/16	2	0.519
25	4227695	1	65	2	1	29-03-2016	Combigan TravoZ	1	3	7	7	19	0.6	23.42	13-10-2016	0	04-11-16	0.00	17	avascular bleb	0	RSR	19-11-16	0.00	14	low bleb	0	LSL	14-12-16	0.00	13	low bleb	0	0	03-05-16	0.00	13	low bleb	0	0	1	0.502
26	4060864	2	67	1	1	15-03-2015	Brimolol	2	4	4	0	20	0.8	24	29-07-2015	0	11-04-16	0.20	12	vascularised bleb	0	RS removed	19-04-16	0.00	14	low bleb	0	0	27-06-16	0.00	18	low bleb	brimolol BE	0	19-09-16	0	11	bleb+	Brimolol BE	0	2	0.437
27	4147546	1	61	2	1	19-10-2013	Brimocom e/d + Tovaxo 19/10/15	1	3	36	5	14	0.8	22.59	23-03-2016	0	07-04-16	0.00	12	vascularised bleb	0	RS removed	25-04-16	0.20	16	bleb+	0	RS removed	21-05-16	0.20	20	bleb+	0	LSL	30-01-16	0	17	fibrosed bleb	since 25/4/16	0	2	0.486
28	2277099	1	66	1	1	05-05-2011	Travocom Brinolar	1	3	120	72	10	0.6	23.28	23-03-2016	0	04-04-16	0.00	18	vascularised bleb	0	LSL	11-04-16	0.20	5	bleb+	0	0	25-04-16	0.20	10	bleb+	0	0	07-02-16	0	14	bleb+	0	0	1	0.565
29	2704537	1	65	1	2	since 2011	Iotim Careprost	1	3	60	60	22	1.08	22.59	24-03-2016	0	18-04-16	0.00	10	low bleb	0	0	18-04-16	0.00	20	bleb+	0	LSL	28-04-16	0.00	12	bleb+	0	LSL	22-12-16	0	16	flat bleb	0	0	1	0.546
30	3395218	2	66	1	1	13-11-2014	Brimolol Monosopt	2	4	24	0	16	0.2	23.64	24-03-2016	0	07-04-16	0.20	16	vascularised bleb	0	LSL	26-04-16	0.20	10	bleb+	0	0	10-05-16	0.20	6	bleb+	0	0	07-12-16	0.2	18	flat bleb	0	0	1	0.543
31	3426563	1	68	1	1	since 2004	Careprost Brinzox 2014	1	3	144	144	14	0.8	23.2	24-03-2016	0	15-04-16	0.20	12	flat bleb	0	LSL	15-04-16	0.00	12	low bleb	0	LSL	29-04-16	0.00	15	low bleb	0	0	25-01-16	0	15	low bleb	0	0	1	0.535
32	3811489	2	66	2	2	since 2011	Careprost	1	1	60	60	17	0.3	24.17	25-03-2016	0	09-04-16	0.00	9	diffuse bleb	0	0	19-04-16	0.00	12	tenons cyst	0	RS removed	30-04-16	0.00	13	tenons cyst	0	Tenons cyst - needling on 30/7/16	05-01-17	0	15	bleb+	0	0	2	0.502
33	4228421	1	65	2	1	since 2014	Timolet	2	2	24	0	17	0.3	22.61	26-08-2016	0	25-03-16	0.30	14	bleb+	0	0	09-04-16	0.30	12	bleb+	0	0	26-04-16	0.30	12	flat vascularised bleb	0	LSL	16-07-16	0.2	12	bleb+	0	0	1	0.568
34	3924751	2	78	1	2	22-11-2014	Timolet	2	2	24	0	13	0.6	24.12	31-03-2016	0	15-04-16	0.02	10	vascularised bleb	0	LSL	29-04-16	0.02	11	bleb+	0	LSL	24-05-16	0.20	8	bleb+	0	0	22-12-16	0.2	9	bleb+	0	0	1	0.535
35	3779547	2	56	1	1	09-04-2014	Timolet	2	2	24	0	16	0.2	22.56	01-04-2016	0	02-05-16	0.00	13	diffuse bleb	0	LSL	18-07-16	0.00	18	low bleb	0	LSL	18-08-16	0.00	18	low bleb	0	0	18-09-16	0	12	bleb+	0	0	1	0.535
36	4236318	1	68	1	1	11-07-2013	Iotim e/d BE	2	2	36	0	20	0.8	23.53	01-04-2016	0	15-04-16	0.20	11	low bleb	0	0	25-04-16	0.20	10	low bleb	0	LSL	30-04-16	0.20	10	vascularised bleb	0	LSL	18-05-16	0.2	8	low bleb	0	0	1	0.519
37	3292957	1	68	1	2	19-12-2011	Lumigan e/d Combigan 2012	1	3	60	60	12	0.3	23.41	05-04-2016	0	21-04-16	0.00	16	bleb+	0	RSR	05-05-16	0.00	14	bleb+	0	apical LSL	24-05-16	0.00	8	bleb+	0	0	30-01-17	0	6	bleb+	0	0	1	0.469
38	3802281	1	56	2	1	23-04-2015	Glucomol BD	2	2	12	0	19	0.5	22.1	07-04-2016	0	18-04-16	0.00	9	low bleb	0	0	28-04-16	0.00	12	0	0	RSR	01-06-16	0.20	13	low bleb	0	LSL	19-07-16	0.2	12	low bleb	0	0	1	0.486
39	3821151	2	69	1	2	09-06-2014	Glucomol BD	2	2	24	0	15	0.3	23.85	09-04-2016	0	23-04-16	0.00	20	low bleb	0	RSR	09-05-16	0.00	14	fibrosed bleb	Betabrim e.d	LSL	01-07-16	0.00	12	low fibrosed bleb	Betabrim e.d	LSL	22-11-16	0	13	low bleb	Betabrim e.d	RSR	2	0.535
40	4139310	1	61	1	1	06-10-2015	Bimat TCibrim Z	1	3	6	6	38	0.6	24.16	15-04-2016	0	07-05-16	0.60	12	low bleb	0	0	08-06-16	0.50	17	bleb+	0	LSL	LOST FOR FOLLOW-UP												0	0.568
41	2276492	2	60	2	1	30-08-2007	Lumigan Alphagan 2014	1	3	108	108	16	0.3	23.03	16-04-2016	0	22-04-16	0.00	30	bleb raised on digital massage	0	0	28-04-16	0.00	18	low vascularised bleb	0	LSL	LOST FOR FOLLOW-UP												0	
42	4241263	1	55	2	1	15-01-2016	Lopres e.d BD	2	2	3	0	18	1	23.44	19-04-2016	0	10-05-16	0.00	12	mild conjunctival retraction	0	1RSR	24-05-16	0.00	12	conjunctival retraction	12	LSL	23-06-16	0.00	14	vascularised bleb	0	LSL	07-11-16	0	12	low bleb	0	0	1	0.537

43	4238872	2	48	2	1	2011	Iotim e/d	2	2	60	0	30	1	23.93	29-03-2016	0	12-04-16	0.00	26	bleb raised on digital massage	0	2RS removed	27-04-16	0.00	15	low bleb		apical LSL	11-05-16	0.00	24	flat bleb		Bleb needling(11/5/16)	08-12-16	0	16	flat bleb	Combigan BD, Travatan e/d HS	0	2	0.519
44	4092202	1	68	1	1	29-01-2015	Combigan	2	4	12	0	14	0.5	26.96	03-05-2016	0	18-05-16	0.00	11	low bleb	0	0	04-06-16	0.00	10	diffuse bleb	0	0	27-06-16	0.00	8	diffuse bleb	0	0	21-09-16	0	8	bleb+	0	RS removal	1	0.535
45	802956	1	63	1	1	10-04-2009	Careprost Iobrim	1	3	84	84	12	0.6	25.1	10-05-2016	0	25-05-16	0.00	26	low diffuse vascularised bleb	0	RSR	03-06-16	0.00	28	thick walled flat vascularised bleb	0	LSL	13-06-16	0.00	22	flat vascularised bleb	Iobrim TID	Bleb needling (6/8/16)	04-11-16	0	12	low bleb	Lopres e/d BD	0	2	0.502
46	4198723	1	75	2	2	12-11-2015	Betabrim BD, Dorzox TDS	2	4	3	0	20	1.08	23.04	12-02-2016	0	01-03-16	0.00	32	flat bleb	0	apical suture	18-05-16	0.00	21	bleb+	Cibrim Z BD	0	07-06-16	0.00	20	low bleb	Cibrim Z bd and Dorzox TID	loose suture removal	21-02-17	0	20		AlphaganP + Tovaxo	0	2	0.551
47	4198723	2	75	2	2		Betabrim BD, Dorzox TDS	2	4	4	0	21	0.6	23.01	11-05-2016	early FM, shallow AC	20-05-16	0.30	9	vascularise bleb choroidal folds	Flupred e/d QID	360d shallow CD	07-06-16	0.00	20	low bleb	Alphagan P BE		06-09-16	0.00	18		Alphagan P bd	0		0	17		AlphaganP		2	0.548
48	4145012	2	60	2	1	01-06-2015	Duobrom Travatan	1	3	4	4	16	1	22.1	17-10-2015	0	30-05-16	0.00	14	bleb+	LOST FOR																				0	0.502
49	4004382	2	71	2	2	29-04-2015	Combigan	2	4	12	0	20	0.5	21.91	31-05-2016	0	15-06-16	0.00	13	vascularised bleb	0	LSL	30-06-16	0.00	22	flat bleb	0	LSL	15-07-16	0.00	16	flat bleb	0	0	20-08-16	0	12	flat bleb	0	0	1	0.519
50	3835900	1	63	1	1	30-06-2014	Combigan	2	4	24	0	21	0.8	23.36	18-08-2016	0	02-09-16	0.00	20	low bleb	0	1RS	23-09-16	0.00	15	bleb+	0	RSR	04-10-16	0.00	18	low bleb	0	LSL	15-02-17	0	19	flat bleb	0	0	1	0.502
51	3490176	1	75	2	1	13-06-2013	Brinolar	2	2	36	0	21	0.8	23.59	18-08-2016	0	02-09-16	0.00	10	low bleb	0	0	09-09-16	0.00	16	low bleb	0	1RSR	23-09-16	0.00	9	0	0	0	30-01-17	0	12	low bleb	0	0	1	0.535
52	2565337	2	64	2	1	05-08-2015	Combigan BD	2	4	12	0	16	0.5	22.76	26-08-2016	0	08-09-16	0.00	15	low bleb	0	RSR	17-09-16	0.00	17	low bleb, localised DM strip	0	LSL	01-10-16	0.00	15	bleb+	0	0	09-12-16	0	10	low bleb	0	0	1	0.56
53	1969420	2	68	1	1	07-02-2014	Timoblu e/d	2	2	24	0	17	0.2	22.71	22-09-2016	0	07-10-16	0.00	12	vascularised bleb	0	LSL	14-10-16	0.00	17	low bleb, iris in ostium s/p LSL	0	0	18-10-16	0.00	15	low bleb, peaking pupil	Iris repositioning on 21/10/16	0	12-11-16	0	13	low bleb	0	0	1	0.568
54	2299676	1	65	1	1	23-05-2008	Careprost Brimosun	1	3	96	96	16	0.6	22.5	21-09-2016	0	06-10-16	0.00	18	bleb+	0	RSR	LOST FOR FOLLOW UP																		0	0.502
55	4077389	1	57	2	1	08-07-2015	Latoprost RT Lopres 16/3/16	1	3	12	12	21	15	22.57	21-10-2016	0	09-11-16	0.00	12	bleb not raised by massage	0	LSL	23-11-16	0.00	12	low bleb	0	add LSL	25-01-17	0.00	14	low bleb	0	0	25-05-17	0.00	14	low bleb	0	0	1	0.549
56	3376630	1	81	1	2	30-06-2016	Lopres 0.5% Alphagan Z 27/7/16	2	4	4	0	20	1.07	22.7	14-10-2016	0	25-10-16	0.00	26	vascularised bleb	0	LSL	10-11-16	0.00	9	bleb not raising - vascularised	0	apical LSL	10-12-16	0.00	12	bleb+	0	0	10-04-17	0.00	12	bleb+	0	0	1	0.471
57	4290004	1	45	1	1	24-05-2016	Brimocom e/d Travo z 1/7/16	1	3	5	3	16	1	22.62	22-10-2016	0	07-11-16	0.00	17	bleb+	0	0	18-11-17	0.00	18	bleb not raise with massage	0	LSL	20-12-16	0.00	18	bleb+	0	LSL	20-04-17	0.00	18	bleb+	0	0	1	0.551
58	4366420	1	68	1	1	30-07-2016	Combigan e/d	2	4	3	0	16	1	24.5	13-10-2016	0	04-11-16	0.20	23	avascular bleb	0	LSL	18-11-16	0.20	11	bleb+	0	LSL	02-12-16	0.00	12	good bleb	0	0	16-02-17	0	12	good bleb	0	0	1	0.535
59	4227695	2	65	2	1	25-02-2016	Alphagan Z stopped	1	3	4	3	16	0.6	23.35	30-06-2016	0	21-07-16	0.00	13	bleb on pressure	0	RSR	01-08-16	0.00	12	diffuse bleb	0	RSR	15-08-16	0.00	15	bleb+	0	LSL	14-12-16	0	10	good bleb	0	0	1	0.486
60	4349283	2	60	1	1	08-07-2016	Travoz+Brimolol	1	3	12	3	22	0.5	24.76	18-10-2016	0	07-11-16	0.00	16	vascularised bleb	0	LSL	21-11-16	0.00	12	low bleb	0	0	09-12-16	0.00	16	low bleb	0	LSL	09-01-17	0	16	raised mildly vascularised bleb	0	0	1	0.502
61	4374851	1	47	2	1	01-01-2014	Combigan and Brinolar	2	4	24	0	10	1	23.02	15-10-2016	0	25-10-16	0.20	15	flat bleb	0	1RS	07-11-16	0.20	12	low bleb	0	RSR	12-12-16	0.20	8	low bleb	0	0	16-01-17	0.2	8	low bleb	0	0	1	0.519
62	3376630	1	76	1	2	30-06-2016	Lopres	2	2	4	0	18	0.5	22.7	14-10-2016	0	25-10-16	0.00	26	low vascularised bleb	0	LSL	10-11-16	0.00	9	vascularised bleb	0	LSL	10-12-16	0.00	12	bleb	0	0	14-04-17	0.00	12	bleb	0	0	1	0.472
63	4098634	1	65	1	1	07-01-2016	Combigan	2	4	7	0	28	0.6	23.58	03-08-2016	0	11-08-16	0.20	24	flat bleb with vascularization	0	RSR	22-08-16	0.20	18	bleb+	0	RSR	08-09-16	0.00	14	low bleb	0	LSL	23-09-16	0	14	diffuse bleb	0	0	1	0.469
64	3974337	2	71	2	1	15-04-2015	Timolet Alphagan Z	2	4	12	0	24	0.5	22.97	24-11-2016	0	09-12-16	0.20	16	low bleb	0	LSL	20-12-16	0.00	16	low bleb	Lopres BD	0	10-01-17	00-01-00	14.00	low bleb	Lopres BD	0	10-05-17	0	12	low bleb	Lopres BD	0	2	0.536
65	4262813	1	64	1	2	30-05-2016	Latacom CF	1	1	7	7	9	0.2	23.13	10-12-2016	0	26-12-16	0.20	12	diffuse bleb	0	0	10-01-17	0.00	8	diffuse bleb	0	0	24-01-17	0.00	10	diffuse bleb	0	0	17-02-17	0.2	10	diffuse bleb	0	0	1	0.47
66	2498075	2	45	1	1	15-11-2007	Combigan+ Latomost	1	3	108	108	17	0.5	23.43	25-11-2016	0	05-12-16	0.50	2	diffuse bleb SHALLOW CD	0	0	15-12-16	0.20	14	low vascularised bleb	0	LSL	22-12-17	0.00	31	cystic bleb	Combigan Latoprost	LSL	14-02-17	0	10	bleb+	Cibrim T& Auroprost RT	0	2	0.502
67	2142189	1	66	1	1	05-11-2005	Latoprost Iobrim	1	3	132	120	10	0.5	23.35	27-08-2016	0	12-09-16	0.20	16	bleb+	0	RSR	26-09-16	0.00	19	bleb not raised	0	RSR LSL	13-10-16	0.00	19	bleb+	0	apical LSL	24-01-17	0	14	low bleb	0	0	1	0.519
68	4391938	2	50	2	1	21-08-2016	TravoT	1	1	3	3	36	0.3	22.96	01-11-2016	0	12-11-16	0.20	16	bleb	0		21-11-16	0.20	18	good diffuse bleb	0	RSR	10-03-17	0.30	20	low diffuse bleb	0	apical LSL	10-04-17	0.30	16	low diffuse bleb	0	0	1	0.453
69	4325781	2	52	1	1	05-07-2016	Timolet 0.5%	2	2	4	0	20	1	25.72	23-11-2016	0	02-12-16	0.20	18	low bleb	0	RSR	09-12-16	0.20	15	bleb+	0	LSL							LOST TO FOLLOWUP						0	0.519
70	3643583	1	53	2	1	19-08-2013	Timolet	2	2	36	0	16	0.2	23.41	29-11-2016	0	14-12-16	0.00	8	bleb	0	0	26-12-16	0.00	8	good bleb	0	0	02-01-17	0.00	11	good diffuse bleb	0	0	11-02-17	0	12	bleb+	RSR	0	1	0.486
71	4273791	1	71	1	2	03-05-2016	Betabrim	2	4	7	0	22	0.2	22.47	22-12-2016	0	07-01-17	0.20	12	bleb+	0	LSL	18-01-17	0.20	22	good bleb+	0	LSL	02-02-17	0.20	18	good bleb	0	RSR	02-03-17	0.2	20	bleb+	0	LSL	1	0.551
72	2651661	1	54	2	1	05-01-2015	Travo Z	1	1	19	19	18	0.6	22.27	28-08-2016	0	07-09-16	0.20	18	vascularised bleb	0	LSL	21-09-16	0.00	14	vascularised bleb	0	LSL	21-10-16	0.00	14	avascular bleb	Misopt e/d BE	RSR	19-01-17	0	12	bleb+	Tovaxo T HS	0	2	0.486
74	2757272	1	61	1	1	14-04-2015	Latoprost Timolol	1	3	16	16	39	0.3	23.67	22-09-2016	0	Case sheet not available																								0	
75	3918480	2	59	2	1	14-02-2015	Brimocom Dortas 5/5/16 Auroprost RT	1	3	24	4	13	1	23.66	10-09-2016	0	09-09-16	0.20	13	vascularised bleb	0	RSR	03-10-16	0.20	18	low bleb	0	LSL	22-11-16	0.2	13	avascualar bleb	0	0	22-03-17	0.2	20	bleb+	Brimocom BD	0	2	0.519
76	4236626	1	73	1	2	17-06-2016	Travo combigan Dorzox	1	3	3	3	10	0.3	22.88	03-09-2016	0	28-09-16	0.30	10	vascularised low bleb	0	LSL	26-10-16	0.20	12	low bleb	0	0	LOST FOR FOLLOW-UP												0	0.453
77	4431267	1	55	2	1	29-11-2016	Glucomol BD	2	2	4	0	16	0.6	21.85	31-03-2017	0	11-04-17	0.20	18	bleb not raised on digital massage	0	LSL	25-04-17	0.20	16	low bleb	0	LSL	09-05-17	0.00	16	low bleb	0	0	30-06-17	0	15	bleb+	0	0	1	0.502

78	2720431	2	55	1	1	20-01-2009	Ganfort Dorzox 14/7/15 Xalacom HS	1	3	84	84	20	0.5	24.66	18-02-2017	0	27-03-17	0.00	23	flat vascular bleb	0	0	06-04-17	0.00	22	bleb+	0	Goniopuncture	20-04-17	0.00	16	no bleb	Cibrim T	0	29-06-17	0	18	bleb+	Cibtim T	0	2	0.561
79	4405629	1	53	1	1	22-10-2016	Lopress	2	2	5	0	18	0.8	24.98	16-03-2017	0	07-04-17	0.00	13	vascularised bleb	0	LSL	22-04-17	0.00	10	bleb	0	0	25-05-17	0.00	10	low bleb	0	RSR	22-07-17	0	12	bleb	0	0	1	0.551
80	4446514	2	75	1	1	Dec-16	Bidin LS	2	2	4	0	14	0.3	23.26	19-04-2017	0	05-05-17	0.00	16	low bleb	0	LSL	22-05-17	0.00	4	diffuse bleb	0	0	07-06-17	0.00	4	diffuse bleb	0	0	07-07-17	0	10	diffuse bleb	0	0	1	0.551
81	4121853	2	68	2	1	11-06-2015	Misopt	2	2	9	0	20	0.6	22.72	16-03-2017	0	01-03-17	0.00	16	elevated flat vascularised bleb	0	LSL	15-03-17	0.00	11	vascularised bleb	0	LSL	01-07-17	0.00	10	low bleb	0	0	01-08-17	0.00	10	low bleb	0	0	1	0.535
82	3487105	2	53	1	1	2013	Travo Z, Timolet OD	1	3	48	48	23	0.3	23.68	25-04-2017	0	11-05-17	0.00	22	diffuse bleb	0	RSR	25-05-17	0.00	16	mild conjunctival retraction	0	LSL	13-07-17	0.00	12	avascular bleb	0	0	11-08-17	0.00	13	avascular bleb	0	0	1	0.502
83	4309759	2	81	1	2	18-05-2016	shift to Betabrim Dorzox	2	4	3	0	20	0.5	22.73	11-08-2016	0	24-08-16	0.20	12	bleb on pressure	0	0	13-09-16	0.20	12	low bleb+	0	anchoring suture release	11-10-16	0.20	12	low bleb	0	SR	19-12-16	0.2	12	low bleb	0	0	1	0.519
84	4476117	2	67	1	1	2015	Combigan	2	4	24	0	18	0.5	22.74	16-03-2017	0	01-04-17	0.00	19	bleb raised on digital massage	0	LSL	21-04-17	0.00	20	bleb fibrosis	Combigan	0	11-07-17	0.00	13	fibrosed bleb	Combigan BD	0	07-08-17	0	15	fibrosed bleb	Comigan BD	0	2	0.545
86	3530522	2	61	2	1	2014	Dortas T	2	4	36	0	16	0.8	22.91	06-11-2016	0	21-01-16	0.00	19	diffuse bleb	0	RSR	04-02-16	0.00	11	diffuse bleb with mild vascularisation	0	0	02-03-16	0.00	13	bleb+	0	0	12-07-17	0	19	diffuse bleb	Lopres	0	2	0.486
87	3825640	1	60	1	1	30-07-2014	Brimolol Latoprost RT	1	3	24	24	12	0.3	23.26	09-01-2016	0	25-01-16	0.00	20	flat bleb	0	RSR	09-02-16	0.00	20	flat bleb+	0	RSR	03-03-16	0.00	16	low bleb	0	LSL	28-06-16	0	13	low bleb	0	0	1	0.519
88	4189015	1	73	1	1	28-10-2015	Dorsum T	2	4	3	0	18	0.6	22.6	09-01-2016	0	18-01-16	0.20	19	low bleb	0	RSR	25-01-16	0.00	12	low bleb	0	0	08-02-16	0.00	14	bleb+	0	0	11-08-16	0	20	low bleb	Auroprost RT	0	2	0.502
89	3066215	1	76	1	1	07-05-2015	Misopt	2	2	8	0	14	0.2	22.4	09-01-2016	0	23-01-16	0.30	10	low vascularised bleb	0	RSR	04-02-16	0.20	10	low bleb	0	RSR	18-02-16	0.20	14	flat bleb	0	LSL	31-01-17	0.2	10	low bleb	0	0	1	0.486
90	3990442	2	68	1	1	05-03-2015	Brimolol	2	4	10	0	18	1	23.38	08-01-2016	0	23-01-16	0.20	24	bleb+	0	LSL	09-02-16	0.00	18	low bleb	0	LSL	09-03-16	0.00	13	bleb+	0	0	16-06-16	0	7	bleb+	0	0	1	0.551
91	4118987	1	62	1	2	2013	Auroprost RT	1	3	36	36	20	0.6	23.18	11-01-2016	0	26-01-16	0.20	17	bleb raised on digital massage	0	LSL	12-02-16	0.20	8	bleb+	0	0	12-03-16	0.20	12	bleb+	0	LSL	28-12-16	0.2	18	elevated bleb	0	0	1	0.497
92	4162454	1	46	1	1	16-10-2015	Brimolol	2	4	3	0	10	0.2	24.32	12-01-2016	0	27-01-16	0.00	14	bleb+	0	RSR	11-02-16	0.00	13	low bleb	0	RSR	09-03-16	0.00	20	?tenons cyst	0	Bleb needling	11-08-16	0	16	low bleb	0	0	2	0.495
93	4133959	1	70	2	1	30-09-2015	Iobrim	2	2	4	0	11	0.8	22.42	12-01-2016	0	23-01-16	0.20	10	flat bleb	0	LSL	06-02-16	0.20	10	low bleb	0	LSL	20-02-16	0.20	14	bleb+	0	LSL	11-08-16	0.2	8	good bleb+	0	0	1	0.502
94	4188706	2	58	1	1	28-10-2015	Brimolol	2	4	3	0	28	1.01	22.67	19-01-2016	cheese wiring flap	03-02-16	0.20	28	vascularised bleb	0	RSR	17-02-16	0.00	28	low bleb	0	LSL	04-03-16	0.00	26	fibrosed bleb	0	LSL	17-03-16	0	24	low bleb	Combigan and Dorzox	Bleb needling	2	0.584
95	4185201	2	61	2	1	23-12-2015	Aurotim e/d	2	2	9	0	11	0.8	22.89	15-09-2016	0	30-09-16	0.20	9	flat bleb	0	LSL	07-10-16	0.20	10	diffuse bleb	0	0	24-10-16	0.00	10	bleb +	0	LSL	27-01-17	0	15	bleb+	0	0	1	0.47
96	4095110	2	74	1	1	03-08-2015	Timolet OD	2	2	5	0	20	0.6	22.97	19-01-2016	0	03-02-16	0.20	20	vascularised bleb	0	RSR	10-02-16	0.20	15	good bleb	0	LSL	02-03-16	0.20	16	good bleb	0	0	02-06-16	0.20	15	good bleb	0	0	1	0.535
97	4185201	1	61	2	1	23-12-2015	Aurotim e/d	2	2	3	0	10	0.6	22.99	23-01-2016	0	08-02-16	0.20	12	low bleb	0	RSR	17-02-16	0.20	7	bleb +	0	LSL	31-03-16	0.20	12	flat bleb	0	0	23-06-16	0.2	18	bleb+	0	0	1	0.47
98	3907685	1	57	2	1	27-11-2014	Auroprost RT e/d	2	4	24	24	14	0.5	22.04	08-02-2016	0	08-02-16	0.30	16	vascularised bleb	0	LSL	22-02-16	0.30	16	flat bleb	0	LSL	15-04-16	0.30	13	bleb+	0	0	17-10-16	0.3	14	bleb+	0	0	1	0.502
99	4129116	1	82	1	1	24-09-2015	Betabrim	2	4	4	0	17	0.3	23.06	28-01-2016	0	08-02-16	0.20	12	bleb+	0	LSL	19-02-16	0.20	11	bleb+	0	LSL	21-04-16	0.00	12	bleb+	0	0	12-05-17	0	15	bleb	0	0	1	0.535
100	2384819	2	69	1	1	05-08-2015	Alphagan P	2	2	4	0	20	0.2	22.63	21-01-2016	0	17-02-16	0.00	16	low bleb	0	LSL	09-03-16	0.00	16	low bleb	0	LSL	06-04-16	0.00	13	flat bleb		Nuclear fragment removal	09-08-17	0	13	low bleb	0	0	1	0.551
101	2286967	2	63	2	1	08-10-2008	Ganfort	1	3	96	96	20	0.5	24.61	20-01-2016	0	04-02-16	0.00	23	low bleb	0	LSL	16-02-16	0.00	22	bleb fibrosis	0	LSL	26-02-16	0.00	20	low bleb	Ganfort	LSL	16-06-16	0	12	low bleb	Ganfort	0	2	0.519
102	4182805	1	81	2	1	19-10-2015	Glucomol	2	2	3	0	16	0.8	23.06	20-01-2016	0	04-02-16	1.00	30	bleb+	Glucomol	LSL	11-02-16	1.00	12	bleb+	Glucomol	LSL	18-02-16	1.00	10	bleb	0	LSL	11-05-16	1	13	low bleb	0	0	3	0.502
103	4138183	1	69	2	1	05-10-2015	Glucomol	2	2	4	0	15	0.6	24.9	26-02-2016	0	10-02-16	0.20	11	vascularised bleb	0	RSR	22-02-16	0.20	22	low bleb	0	LSL	07-03-16	0.20	12	diffuse bleb	0	0	08-08-16	0.2	14	bleb+	Bidin T	0	2	0.535
104	3001234	2	69	1	1	04-05-2015	Ganfort	1	3	8	8	18	0.6	23.76	23-01-2016	0	11-02-16	0.30	25	vascularised bleb	0	RSR	01-03-16	0.20	15	bleb+	0	0	13-08-16	0.00	48	diffuse bleb	Azopt e/d BD, lopar SR	0	26-09-16	0	38	bleb+	Alphagan Z, Ganfort, Azopt	AADI	3	0.519
105	4198974	2	65	1	1	28-11-2015	Latoprost RT Bidin	1	3	3	3	19	0.6	22.98	05-02-2016	0	20-02-16	0.00	20	low bleb	0	RSR	01-03-16	0.00	28	flat bleb	0	LSL	08-03-16	0.00	16	low diffuse bleb	0	LSL	23-03-16	0	18	diffuse bleb	0	LSL	1	0.535
106	4092704	2	64	2	1	05-09-2015	Betabrim	2	4	4	0	18	0.6	22.41	27-01-2016	0	11-02-16	0.20	15	diffuse bleb	0	RSR	02-03-16	0.00	20	broken RS	0	LSL	24-03-16	0.00	18	diffuse bleb	0	LSL	13-04-16	0	15	avascular bleb	Lacoma PF	0	2	0.545
107	3826287	2	50	1	1	16-08-2014	Combigan	2	4	5	0	24	0.8	22.59	27-01-2016	0	11-02-16	0.20	18	bleb+	0	RSR	26-02-16	0.00	14	good bleb	0	0	08-03-16	0.00	14	avascular bleb	0	0	01-07-16	0	15	bleb+	0	0	1	0.555
108	4161022	1	76	2	1	13-11-2015	Bidin LS	2	2	3	0	16	1.01	22.94	02-02-2016	0	10-02-16	0.00	12	vascularised bleb	0	0	17-02-16	0.00	13	low bleb	0	LSL	02-03-16	0.00	18	low bleb	0	LSL	03-09-16	0	13	bleb+	Bidin LS	0	2	0.491
109	4309759	1	81	1	2	18-07-2016	shift to Betabrim	2	4	8	0	19	0.5	22.98	21-03-2017	0	05-04-17	0.20	20	low bleb	0	LSL	20-04-17	0.00	12	bleb+	0	0	27-03-16	0.00	14	bleb+	0	0	26-07-16	0.00	13	bleb+	0	0	1	0.519
110	3990442	1	68	1	1	09-04-2015	Dortas	2	4	14	0	16	0.5	23.55	26-06-2016	0	18-07-16	0.00	30	flat bleb	0	LSL	01-08-16	0.00	16	avascular bleb	0	LSL	23-08-16	0.00	10	avascular bleb	0	0	15-10-16	0	9	avascular bleb	0	0	1	0.535
111	4118987	1	62	1	2	2013	Auroprost Rt 7/9/15 add Betabrim and Dortas	1	3	36	36	15	0.8	23.2	14-05-2016	0	10-06-16	0.20	20	bleb+	0	LSL	28-06-16	0.20	16	bleb+	0	0	28-07-16	0.20	15	bleb+	0	0	28-12-16	0	20	elevated bleb	0	0	1	0.501